BC

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 213/81, 213/75, 213/89, 213/61, 401/12, 405/12, 409/12, 413/12, 413/14, 417/12, A61K 31/44

A1

(11) International Publication Number: WO 97/03967

(43) International Publication Date: 6 February 1997 (06.02.97)

(21) International Application Number: PCT/GB96/01746

(22) International Filing Date: 22 July 1996 (22.07.96)

(30) Priority Data:

9515058.7	22 July 1995 (22.07.95)	GB
9515729.3	1 August 1995 (01.08.95)	GB
9604531.5	2 March 1996 (02.03.96)	GB
60/014,212	27 March 1996 (27.03.96)	US

(71) Applicant (*for all designated States except US*): RHONE-POULENC RORER LIMITED [GB/GB]; RPR House, 52 St. Leonards Road, Eastbourne, East Sussex BN21 3YG (GB).

(72) Inventors; and

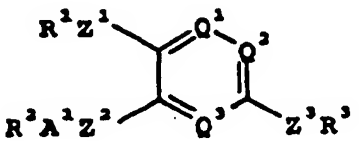
(75) Inventors/Applicants (*for US only*): ALDOUS, David, John [US/GB]; Rhone-Poulenc Rorer Limited, Rainham Road South, Dagenham, Essex RM10 7XS (GB). SMITH, Graham, Frank [GB/GB]; Rhone-Poulenc Rorer Limited, Rainham Road South, Dagenham, Essex RM10 7XS (GB). ASTLES, Peter, Charles [GB/GB]; Rhone-Poulenc Rorer Limited, Rainham Road South, Dagenham, Essex RM10 7XS (GB). PICKETT, Stephen, Dennis [GB/GB]; Rhone-Poulenc Rorer Limited, Rainham Road South, Dagenham, Essex RM10 7XS (GB). McLAY, Iain, McFarlane [GB/GB]; Rhone-Poulenc Rorer Limited, Rainham Road South, Dagenham, Essex RM10 7XS (GB). STUTTLE, Keith, Alfred, James [GB/GB]; Rhone-Poulenc Rorer Limited, Rainham Road South, Dagenham, Essex RM10 7XS (GB). RATCLIFFE, Andrew, James [GB/GB]; Rhone-Poulenc Rorer Limited, Rainham Road South, Dagenham, Essex RM10 7XS (GB).

(74) Agent: CAFFIN, Lee; Rhone-Poulenc Rorer Limited, Patent Dept., Rainham Road South, Dagenham, Essex RM10 7XS (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: SUBSTITUTED AROMATIC COMPOUNDS AND THEIR PHARMACEUTICAL USE



(I)

(57) Abstract

The invention describes compounds of formula (I), wherein R^1 is optionally substituted alkyl, or when Z^1 is a direct bond R^1 may also represent hydrogen; R^2 is optionally substituted aryl, partially saturated bicycloaryl, heteroaryl or R^aR^bN-; R^3 is optionally substituted aryl or heteroaryl group; A^1 is a bond, optionally substituted C_{1-6}alkylene, or C_{2-6}alkylene containing a double or triple bond, or interrupted by oxygen, sulphur, phenylene, imino, alkylimino, sulphinyl or sulphonyl; Z^1 is oxygen, sulphur or a bond; Z^2 is oxygen, sulphur or a bond; Z^3 is -C≡C-, -CH_2-CZ-, -CZ-CH_2-, -CZ-CZ-, -CH_2-NH-, -CH_2-O-, -CH_2-S-, -CH_2-SO-, -CH_2-SO_2-, -CF_2-O-, -CZ-NH-, -NH-CH_2-, -O-CH_2-, -S-CH_2-, -SO-CH_2-, -SO_2-CH_2-, -O-CF_2-, -O-CZ-, -NH-CZ-, -N=N-, -NH-SO_2-, -SO_2-NH-, -CZ-CZ-NH-, -NH-CO-O-, -O-CO-NH-, -C(=NOR^c)CH_2-, -C(F)=N-, -CH(F)-CH_2-, or -NH-CO-NH-; Z is oxygen or sulphur; R^a and R^b each independently are alkyl or arylalkyl, or NR^aR^b forms a 4-6 membered cyclic amine which optionally contains an additional heteroatom selected from O, S, NH or NR^c, or is substituted with an oxo group; R^c is alkyl or arylalkyl; Q^1, Q^2 and Q^3 are each CH or CX^1 or N; and X^1 is halogen; and N-oxides thereof, and their prodrugs, pharmaceutically acceptable salts, and solvates (e.g. hydrates), thereof. The invention also describes processes for preparing the compounds of formula (I), pharmaceutical compositions comprising such compounds and their use in therapy as inhibitors of TNF and type IV cyclic AMP phosphodiesterase (PDE).

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic			SE	Sweden
CG	Congo	KR	Republic of Korea	SG	Singapore
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LR	Liberia	SZ	Swaziland
CS	Czechoslovakia	LT	Lithuania	TD	Chad
CZ	Czech Republic	LU	Luxembourg	TG	Togo
DE	Germany	LV	Latvia	TJ	Tajikistan
DK	Denmark	MC	Monaco	TT	Trinidad and Tobago
EE	Estonia	MD	Republic of Moldova	UA	Ukraine
ES	Spain	MG	Madagascar	UG	Uganda
FI	Finland	ML	Mali	US	United States of America
FR	France	MN	Mongolia	UZ	Uzbekistan
GA	Gabon	MR	Mauritania	VN	Viet Nam

SUBSTITUTED AROMATIC COMPOUNDS AND THEIR PHARMACEUTICAL USE

This invention is directed to novel substituted aromatic compounds, their preparation, pharmaceutical compositions containing these compounds, and their pharmaceutical use in the treatment of disease states associated with proteins that mediate cellular activity.

Tumour necrosis factor (TNF) is an important pro-inflammatory cytokine which causes hemorrhagic necrosis of some tumors and possesses other important biological activities. TNF is released by activated macrophages, activated T-lymphocytes, natural killer cells, mast cells and basophils, fibroblasts, endothelial cells and brain astrocytes amongst other cells.

The principal in vivo actions of TNF can be broadly classified as inflammatory and catabolic. It has been implicated as a mediator of endotoxic shock, inflammation of joints and of the airways, immune deficiency states, allograft rejection, and in the cachexia associated with malignant disease and some parasitic infections. In view of the association of high serum levels of TNF with poor prognosis in sepsis, graft versus host disease and adult respiratory distress syndrome, and its role in many other immunologic processes, this factor is regarded as an important mediator of inflammation.

TNF primes or activates neutrophils, eosinophils, fibroblasts and endothelial cells to release tissue damaging mediators. TNF also activates monocytes, macrophages and T-lymphocytes to cause the production of colony stimulating factors and other pro-inflammatory cytokines such as IL_1, IL_6, IL_8 and GM-CSF, which in some cases mediate the end effects of TNF. The ability of TNF to activate T-lymphocytes, monocytes, macrophages and related cells has been implicated in the progression of Human Immunodeficiency Virus (HIV) infection.

In order for these cells to become infected with HIV and for HIV replication to take place the cells must be maintained in an activated state. Cytokines such as TNF have been shown to activate HIV replication in monocytes and macrophages. Features of endotoxic shock such as fever, metabolic acidosis, hypotension and intravascular coagulation are thought to be mediated through the actions of TNF on the hypothalamus and in reducing the anti-coagulant activity of vascular endothelial cells. The cachexia associated with certain disease states is mediated through indirect effects on protein catabolism. TNF also promotes bone resorption and acute phase protein synthesis.

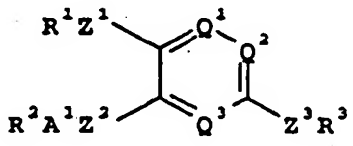
The discussion herein relates to disease states associated with TNF including those disease states related to the production of TNF itself, and disease states associated with other cytokines, such as but not limited to IL_1, or IL_6, that are modulated by and/or associated with TNF. For example, a IL_1 associated disease state, where IL_1 production or action is exacerbated or secreted in response to TNF, would therefore be considered a disease state associated with TNF. TNF-alpha and TNF-beta are also herein referred to collectively as "TNF" unless specifically delineated otherwise, since there is a close structural homology between TNF-alpha (cachectin) and TNF-beta (lymphotoxin) and each of them has a capacity to induce similar biologic responses and bind to the same cellular receptor.

Cyclic AMP phosphodiesterases are important enzymes which regulate cyclic AMP levels and in turn thereby regulate other important biological responses. The ability to regulate cyclic AMP phosphodiesterases, including type IV cyclic AMP phosphodiesterase, therefore, has been implicated as being capable of treating assorted biological conditions. In particular, inhibitors of type IV cyclic AMP phosphodiesterase

have been implicated as being bronchodilators, prophylactic agents useful against asthma and as agents for inhibiting eosinophil accumulation and the function of eosinophils, and for treating other diseases and conditions characterized by, or having an etiology involving, morbid eosinophil accumulation. Inhibitors of cyclic AMP phosphodiesterase are also implicated in treating inflammatory diseases, proliferative skin diseases and conditions associated with cerebral metabolic inhibition.

It has already been reported that certain substituted monocyclic aromatic compounds have valuable pharmaceutical properties, in particular the ability to regulate proteins that mediate cellular activity, for example, type IV cyclic AMP phosphodiesterase, for example in the specifications of International Patent Application Publications Nos. WO 94/12461 and WO 95/01338.

We have now found that certain substituted aromatic compounds have valuable pharmaceutical properties, in particular the ability to regulate proteins that mediate cellular activity, for example, type IV cyclic AMP phosphodiesterase and/or TNF. Thus, in a first aspect of the present invention, there is provided a compound of formula (I)



(I)

wherein

R^1 represents a straight- or branched-chain alkyl group of 1 to about 6 carbon atoms, optionally substituted by one or more halogen atoms, or when Z^1 is a direct bond R^1 may also represent a hydrogen atom;

R^2 represents an optionally substituted aryl, partially saturated bicycloaryl, heteroaryl or R^aR^bN- group;

R^3 represents an optionally substituted aryl or heteroaryl group;

A^1 represents a direct bond, a straight- or branched-chain alkylene linkage containing from 1 to about 6 carbon atoms optionally substituted by halogen, hydroxyl, alkoxy or oxo, or A^1 represents a straight- or branched-carbon chain comprising from 2 to about 6 carbon atoms and contains a double or triple carbon-carbon bond, or is interrupted by an oxygen or sulphur atom, a phenylene, imino (-NH-) or alkylimino linkage, or a sulphinyl or sulphonyl group;

Z^1 represents an oxygen or sulphur atom or a direct bond;

Z^2 represents an oxygen or sulphur atom or a direct bond;

Z^3 represents a -C≡C-, $-CH_2-CZ-$, $-CZ-CH_2-$, -CZ-CZ-, $-CH_2-NH-$, $-CH_2-O-$, $-CH_2-S-$, $-CH_2-SO-$, $-CH_2-SO_2-$, $-CF_2-O-$, -CZ-NH-, $-NH-CH_2-$, $-O-CH_2-$, $-S-CH_2-$, $-SO-CH_2-$, $-SO_2-CH_2-$, $-O-CF_2-$, -O-CZ-, -NH-CZ-, -N=N-, $-NH-SO_2-$, $-SO_2-NH-$, -CZ-CZ-NH-, -NH-CO-O-, -O-CO-NH-, $-C(=NOR^c)CH_2-$, -C(F)=N-, $-CH(F)-CH_2-$, or -NH-CO-NH- linkage;

Z represents an oxygen or sulphur atom;

R^a and R^b each independently represents an alkyl or arylalkyl group, or NR^aR^b forms a 4-6 membered cyclic amine which optionally contains an additional heteroatom selected from O, S, NH or NR^c, or is substituted with an oxo group;

R^c represents an alkyl or arylalkyl group;

Q^1, Q^2 and Q^3, which may be the same or different, each represents a CH or CX^1 linkage or a nitrogen atom; and

X^1 represents a halogen atom;

and N-oxides thereof, and their prodrugs, pharmaceutically acceptable salts, and solvates (e.g. hydrates), thereof;

but excluding compounds of formula (I) where R^1 represents a straight- or branched-chain alkyl group of 1 to about 4 carbon atoms substituted by one or more fluorine atoms, R^2 represents a phenyl group, R^3 represents an optionally substituted phenyl or pyridyl group, A^1 represents methylene group, Q^1, Q^2 and Q^3 each represent a CH linkage, Z^1 and Z^2 each represent an oxygen atom, and Z^3 represents a -CO-NH- linkage, and compounds of formula (I) where R^1 represents methyl, ethyl, difluoromethyl or trifluoromethyl, R^2 represents a phenyl group optionally substituted with C_{1-4}alkyl, C_{1-4}alkoxy or halogen, R^3 represents an optionally substituted aryl or heteroaryl group, A^1 represents a C_{1-6}alkylene (optionally substituted by halogen, hydroxy or alkoxy), a $-OC_{2-6}$alkylene, or a $-NHC_{2-6}$alkylene linkage, Q^1, Q^2 and Q^3 each represent a CH linkage, Z^1 and Z^2 each represent an oxygen atom, and Z^3 represents a $-CH_2-O-$, $-CH_2-NH-$, $-CH_2-S-$, $-O-CH_2-$, $-S-CH_2-$, $-NH-CH_2-$, $-CH_2-CO-$, $-CO-CH_2-$, -CO-NH-, -O-CO- or -NH-CO- linkage.

In the present specification, the term "compounds of the invention", and equivalent expressions, are meant to embrace compounds of general formula (I) as hereinbefore described, which expression includes the N-oxides, the prodrugs, the pharmaceutically acceptable salts, and the solvates, e.g. hydrates, where the context so permits. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their N-oxides, salts, and solvates, where the context so permits. For the sake of clarity, particular instances when the context so permits are sometimes indicated in the text, but these instances are purely illustrative and it is not intended to exclude other instances when the context so permits.

As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:-

"Patient" includes both human and other mammals.

"Alkyl" as a group or part of a group means straight- or branched-chain alkyl. Particular alkyl groups, unless otherwise specified, have 1 to about 12 carbon atoms in the chain, more particularly from 1 to about 6 carbon atoms and include, for example C_{1-4}alkyl groups exemplified by methyl, ethyl, n-propyl, s-propyl, n-butyl, s-butyl and t-butyl.

"Aryl" as a group or part of a group denotes a monocyclic or multicyclic aromatic carbocyclic moiety of about 6 to about 10 carbon atoms. When R^3 represents an optionally substituted aryl group this may particularly represent an aromatic carbocyclic moiety of about 6 to about 10 carbon atoms such as phenyl or naphthyl optionally substituted with one or more aryl group substituents which may be the same or different, where "aryl group substituent" includes, for example, hydrogen, alkyl, aryl, arylalkyl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, arylalkoxy, carboxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, arylalkoxycarbonyl, acylamino, aroylamino, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, alkylthio, arylthio, arylalkylthio, Y^1Y^2N-, Y^1Y^2NCO- or $Y^1Y^2NSO_2$-, where Y^1 and Y^2 are independently hydrogen, alkyl, aryl, and aralkyl. Preferred aryl group substituents include hydrogen, alkyl, hydroxy, acyl, aroyl, halo, nitro, cyano, alkoxycarbonyl, acylamino, alkylthio, Y^1Y^2N-, Y^1Y^2NCO- and $Y^1Y^2NSO_2$-, where Y^1 and Y^2 are independently hydrogen and alkyl. When R^2 contains an optionally substituted aryl group this may particularly

represent a phenyl group optionally substituted by one or more substituents selected from, for example, halogen atoms and alkyl, haloalkyl (for example trifluoromethyl), phenyl, phenylalkyl, hydroxy, hydroxyalkyl, alkoxy, phenoxy, phenylalkoxy, nitro and cyano groups.

"Partially saturated bicycloaryl" means a group in which an aryl and a cycloalkyl group are fused together to form a bicyclic structure. Exemplary arylalkyl groups include indanyl and tetrahydronaphthyl, especially indanyl.

"Arylalkyl" means a group in which the aryl and alkyl moieties are as previously described. Preferred arylalkyl groups contain a C_{1-4}alkyl moiety. Exemplary arylalkyl groups include benzyl, 2-phenethyl and naphthlenemethyl.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyl groups contain C_{1-4}alkyl. Exemplary hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Acyl" as a group or part of a group means an H-CO- or alkyl-CO- group in which the alkyl group is as previously described. Preferred acyl groups contain C_{1-4}alkyl. Exemplary acyl groups include formyl, acetyl, propanoyl, 2-methylpropanoyl, butanoyl and palmitoyl.

"Aroyl" as a group or part of a group means an aryl-CO- group in which the aryl group is as previously described. Exemplary groups include benzoyl and 1- and 2-naphthoyl.

"Y^1Y^2N-" means a substituted or unsubstituted amino group, wherein Y^1 and Y^2 are as previously described. Exemplary

groups include amino (H_2N-), methylamino, ethylmethylamino, dimethylamino and diethylamino.

"Alkoxycarbonyl" means an alkyl-O-CO- group. Exemplary alkoxycarbonyl groups include methoxy- and ethoxycarbonyl.

"Aryloxycarbonyl" means an aryl-O-CO- group. Exemplary aryloxycarbonyl groups include phenoxy- and naphthoxycarbonyl.

"Arylalkoxycarbonyl" means an arylalkyl-O-CO- group. An exemplary arylalkoxycarbonyl group is benzyloxycarbonyl.

"Y^1Y^2NCO-" means a substituted or unsubstituted carbamoyl group, wherein Y^1 and Y^2 are as previously described. Exemplary groups are carbamoyl (H_2NCO-) and dimethylcarbamoyl (Me_2NCO-).

"$Y^1Y^2NSO_2$-" means a substituted or unsubstituted sulfamoyl group, wherein Y^1 and Y^2 are as previously described. Exemplary groups are sulfamoyl (H_2NSO_2-) and dimethylsulfamoyl (Me_2NSO_2-).

"Alkylsulfonyl" means an alkyl-SO_2- group. Preferred groups are those in which the alkyl group is C_{1-4}alkyl.

"Alkylsulfinyl" means an alkyl-SO- group. Preferred groups are those in which the alkyl group is C_{1-4}alkyl.

"Halo" or "halogen" means fluoro, chloro, bromo, or iodo. Preferred are fluoro, chloro or bromo; more preferred are fluoro or chloro.

"Heteroaryl" denotes an aromatic monocyclic or multicyclic organic moiety of about 5 to about 10 ring members in which one

or more of the ring members is/are element(s) other than carbon, for example nitrogen, oxygen or sulphur. Examples of suitable optionally substituted heteroaryl groups include pyrazinyl, furyl, benzofuranyl, thienyl, pyridyl, pyrimidinyl, isoxazolyl, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, thiazolyl, 1,3,4-thiadiazolyl, isothiazolyl, pyridazinyl, 1,2,4-triazinyl, quinolinyl, and isoquinolinyl groups, optionally substituted by one or more aryl group substituents. When R^3 contains an optionally substituted heteroaryl group this may particularly represent an optionally substituted "azaheteroaryl" group (where the term "azaheteroaryl" means a heteroaryl group of about 5 to about 10 ring members in which one or more of the ring members is/are nitrogen). Preferred heteroaryl groups within R^2 include thienyl, thiazolyl, pyridyl, 1,2,4-oxadiazole or 1,3,4-oxadiazole. Optional substituents for the heteroaryl group within R^2 include, for example, halogen atoms and alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, oxo, hydroxyalkyl, haloalkyl (for example trifluoromethyl), alkoxy, haloalkoxy, aryloxy, heteroaryloxy, arylalkoxy and heteroarylalkoxy groups. Preferred heteroaryl groups represented by R^3 are optionally substituted pyridyl groups, especially wherein the optional substituents are alkyl groups or, more particularly, halogen atoms.

"Substituted oxadiazole" denotes substituted by, for example, a halogen atom, or an alkyl, haloalkyl (for example trifluoromethyl), aryl, heteroaryl, arylalkyl, heteroarylalkyl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, heteroaryloxy, arylalkoxy, or heteroarylalkoxy group.

"Prodrug" means a compound which is convertible <u>in vivo</u> by metabolic means (e.g. by hydrolysis) to a compound of formula

(I), including N-oxides thereof, for example an ester of a compound of formula (I) containing a hydroxy group.

Suitable esters are of many different types, for example acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-β-hydroxynaphthoates, gentisates, isethionates, di-p-toluoyltartrates, methanesulphonates, ethanesulphonates, benzenesulphonates, p-toluenesulphonates, cyclohexylsulphamates and quinates.

An especially useful class of esters may be formed from acid moieties selected from those described by Bundgaard et al., J. Med. Chem., 32, (1989), 2503-2507, and include substituted (aminomethyl)-benzoates, for example dialkylamino-methylbenzoates in which the two alkyl groups may be joined together and/or interrupted by an oxygen atom or by an optionally substituted nitrogen atom, e.g. an alkylated nitrogen atom, more especially (morpholino-methyl)benzoates, e.g. 3- or 4-(morpholinomethyl)-benzoates, and (4-alkylpiperazin-1-yl)benzoates, e.g. 3- or 4-(4-alkylpiperazin-1-yl)benzoates.

Some of the compounds of the present invention are basic, and such compounds are useful in the form of the free base or in the form of a pharmaceutically acceptable acid addition salt thereof.

Acid addition salts are a more convenient form for use; and in practice, use of the salt form inherently amounts to use of the free base form. The acids which can be used to prepare the acid addition salts include preferably those which produce, when combined with the free base, pharmaceutically acceptable salts, that is, salts whose anions are non-toxic to the patient in pharmaceutical doses of the salts, so that the beneficial

inhibitory effects inherent in the free base are not vitiated by side effects ascribable to the anions. Although pharmaceutically acceptable salts of said basic compounds are preferred, all acid addition salts are useful as sources of the free base form even if the particular salt, per se, is desired only as an intermediate product as, for example, when the salt is formed only for purposes of purification, and identification, or when it is used as intermediate in preparing a pharmaceutically acceptable salt by ion exchange procedures. Pharmaceutically acceptable salts within the scope of the invention include those derived from mineral acids and organic acids, and include hydrohalides, e.g. hydrochlorides and hydrobromides, sulphates, phosphates, nitrates, sulphamates, acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-β-hydroxynaphthoates, gentisates, isethionates, di-p-toluoyltartrates, methanesulphonates, ethanesulphonates, benzenesulphonates, p-toluenesulphonates, cyclohexylsulphamates and quinates.

As well as being useful in themselves as active compounds, salts of compounds of the invention are useful for the purposes of purification of the compounds, for example by exploitation of the solubility differences between the salts and the parent compounds, side products and/or starting materials by techniques well known to those skilled in the art.

It will be apparent to those skilled in the art that certain compounds of the invention can exhibit isomerism, for example optical isomerism and geometrical isomerism. All such isomers of the compounds of the invention, and their mixtures, are within the scope of the invention.

With reference to formula (I) above, the following are particular and preferred groupings:

R^1 preferably represents a C_{1-4}alkyl group optionally substituted by one or more halogen (e.g. fluorine) atoms. R^1 more preferably represents methyl or difluoromethyl.

R^2 particularly represents an optionally substituted heteroaryl group, preferably optionally substituted thienyl, thiazolyl, pyridyl, oxidopyridinio, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl.

R^2 also particularly represents an optionally substituted aryl group, such as a phenyl or alkoxyphenyl, or preferably a 4-methoxyphenyl, group.

R^2 also particularly represents a partially saturated bicycloaryl group. Preferred bicycloaryl groups contain a cyclopentyl moiety fused to an aryl ring, for example indanyl, especially a 2-indanyl group.

R^2 also particularly represents a R^aR^bN- group, such as a piperidinyl, morpholinyl or pyrrolidinyl, especially 2-oxo-pyrrolidinyl.

R^2 preferably represents substituted 1,2,4-oxadiazolyl or 1,3,4-oxadiazolyl particularly where the substituent is an optionally substituted phenyl group or a heteroaryl (e.g. pyridyl) group.

R^2 more preferably represents substituted 1,2,4-oxadiazol-5-yl or 1,3,4-oxadiazol-5-yl each substituted in the 3- and 2-positions respectively by an optionally substituted phenyl group (e.g. 4-halophenyl or 4-alkoxyphenyl) or more especially substituted in the 3- and 2-positions respectively by a heteroaryl (e.g. pyridyl such as 2-pyridyl) group.

R^3 preferably represents a heteroaryl group substituted on both the positions next to the position which is directly attached to Z^3.

R^3 also preferably represents a heteroaryl group substituted by one or two halogen, e.g. chlorine, atoms.

R^3 more preferably represents an optionally substituted azaheteroaryl group, such as an optionally substituted pyridyl group, especially a pyridyl group substituted by one or two halogen, e.g. chlorine, atoms, particularly where the halogen atom(s) is/are positioned next to the position which is directly attached to the linkage Z^3.

R^3 is especially a 3,5-dihalopyrid-4-yl moiety, more especially a 3,5-dichloropyrid-4-yl moiety.

It is to be understood that the aforementioned heteroaryl moieties represented by R^3 when containing at least one nitrogen atom may be presented as the corresponding N-oxides, and such N-oxides are also preferred. Thus, R^3 may preferably represent a 3,5-dihalo-1-oxido-4-pyridinio group, such as a 3,5-dichloro-1-oxido-4-pyridinio group.

Z^1 preferably represents an oxygen atom.

Z^2 preferably represents an oxygen atom or a bond.

Z^3 preferably represents a -CO-NH-, $-CO-CH_2-$, -C(F)=N- or $-CH(F)-CH_2-$ group.

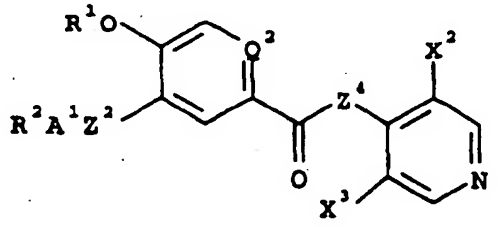
Q^1, Q^2 and Q^3 may particularly each independently represent CH, CX^1, N or N(O). Preferably, Q^1 and Q^3 are CH and Q^2 is CH, CF, N or N(O).

Examples of the moiety A^1 include a direct bond, an unsubstituted straight chain alkylene linkage containing from 1 to 6 carbon atoms, or a straight carbon chain comprising from 2 to 6 carbon atoms and contains a double or triple carbon-carbon bond, or is interrupted by an oxygen atom;

A^1 particularly represents a direct bond, a straight chain alkylene linkage containing from 1 to 4 carbon atoms, i.e. a methylene, ethylene, propylene or butylene linkage, or a straight chain alkylene linkage containing from 3 to 4 carbon atoms interrupted by an oxygen atom especially a $-CH_2OCH_2CH_2-$ or $-OCH_2CH_2-$linkage.

It is to be understood that this invention covers all appropriate combinations of the particular and preferred groupings referred to herein.

A further particular group of compounds of the present invention are compounds of formula (Ia)



(Ia)

wherein R^1, R^2, A^1, Q^2 and Z^2 are as defined previously, X^2 and X^3 each represent a halogen atom, and Z^4 is NH or CH_2, and

N-oxides thereof and their prodrugs, pharmaceutically acceptable salts, and solvates (e.g. hydrates), thereof.

Compounds of formula (Ia) in which R^1 represents methyl or difluoromethyl are preferred.

Compounds of formula (Ia) in which R^2 represents an optionally substituted phenyl (particularly 4-methoxyphenyl), indanyl (particularly 2-indanyl), optionally substituted pyrrolidinyl (particularly 2-oxo-pyrrolidinyl), furyl, thienyl, thiazolyl, pyridyl or pyridazyl group, or a substituted oxadiazole (particularly a 1,2,4- or a 1,3,4-oxadiazole) group are preferred. R^2 is particularly a 3-heteroaryl-1,2,4-oxadiazol-5-yl group such as a 3-pyridyl-1,2,4-oxadiazol-5-yl group, especially 3-(2-pyridyl)-1,2,4-oxadiazol-5-yl.

Compounds of formula (Ia) in which X^2 and X^3 each represent, a fluorine, or more particularly, a chlorine atom are preferred.

Compounds of formula (Ia) in which A^1 a straight chain alkylene linkage containing from 1 to 4 carbon atoms are preferred.

Compounds of formula (Ia) in which A^1 a straight chain alkylene linkage containing from 3 to 4 carbon atoms interrupted by an oxygen atom, especially a $-CH_2OCH_2CH_2-$ or $-OCH_2CH_2-$ linkage, are also preferred.

Compounds of formula (Ia) in which Q^2 represents CH, N or N(O) are preferred.

Compounds of formula (Ia) in which Z^2 represents an oxygen atom or a direct bond are preferred.

A preferred group of compounds of the invention are compounds of formula (Ia) in which R^1 is methyl or difluoromethyl, R^2 is an optionally substituted aryl group, especially phenyl or 4-methoxyphenyl, X^2 and X^3 each represent a chlorine atom, and A^1, Q^2, Z^2 and Z^4 are as defined above, and N-oxides and solvates (e.g. hydrates) thereof.

A further preferred group of compounds of the invention are compounds of formula (Ia) in which R^1 is methyl or difluoromethyl, R^2 is a 2-indanyl group, X^2 and X^3 each represent a chlorine atom, and A^1, Q^2, Z^2 and Z^4 are as defined above, and N-oxides and solvates (e.g. hydrates) thereof.

A further preferred group of compounds of the invention are compounds of formula (Ia) in which R^1 is methyl or difluoromethyl, R^2 is a 2-oxo-pyrrolidinyl group, X^2 and X^3 each represent a chlorine atom, and A^1, Q^2, Z^2 and Z^4 are as defined above, and N-oxides and solvates (e.g. hydrates) thereof.

A further preferred group of compounds of the invention are compounds of formula (Ia) in which R^1 is methyl or difluoromethyl, R^2 is an optionally substituted pyridyl group, especially a 2-pyridyl, 3-pyridyl or 4-pyridyl group or an N-oxide thereof, X^2 and X^3 each represent a chlorine atom, and A^1, Q^2, Z^2 and Z^4 are as defined above, and N-oxides and solvates (e.g. hydrates) thereof.

A further preferred group of compounds of the invention are compounds of formula (Ia) in which R^1 is methyl or difluoromethyl, R^2 is an optionally substituted thienyl group, especially a 2-thienyl group, X^2 and X^3 each represent a

chlorine atom, and A^1, Q^2, Z^2 and Z^4 are as defined above, and N-oxides and solvates (e.g. hydrates) thereof.

A further preferred group of compounds of the invention are compounds of formula (Ia) in which R^1 is methyl or difluoromethyl, R^2 is a 1,2,4-oxadiazol-5-yl group substituted in the 3-position by an optionally substituted phenyl group (e.g. 4-halophenyl or 4-alkoxyphenyl) or substituted in the 3-position by a heteroaryl group (e.g. a pyridyl group such as 2-pyridyl), X^2 and X^3 each represent a chlorine atom, and A^1, Q^2, Z^2 and Z^4 are as defined above, and N-oxides and solvates (e.g. hydrates) thereof.

A further preferred group of compounds of the invention are compounds of formula (Ia) in which R^1 is methyl or difluoromethyl, R^2 is a 1,3,4-oxadiazol-5-yl group, substituted in the 2-position by an optionally substituted phenyl group (e.g. 4-halophenyl or 4-alkoxyphenyl), X^2 and X^3 each represent a chlorine atom, and A^1, Q^2, Z^2 and Z^4 are as defined above, and N-oxides and solvates (e.g. hydrates) thereof.

A particularly preferred group of compounds of the invention are compounds of formula (Ia) in which R^1 is methyl or difluoromethyl, R^2 is a 3-pyridyl-1,2,4-oxadiazol-5-yl group, especially 3-(2-pyridyl)-1,2,4-oxadiazol-5-yl, X^2 and X^3 each represent a chlorine atom, and A^1, Q^2, Z^2 and Z^4 are as defined above, and N-oxides and solvates (e.g. hydrates) thereof.

It is to be understood that the present invention includes compounds of the invention having any combination of the particular and preferred features referred to hereinbefore.

Particular compounds of the invention are selected from the following:

N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(4-phenylbutoxy)benzamide;

N-(3,5-dichloropyridin-4-yl)- 4-methoxy-3-{3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-ylmethoxy}benzamide;

3-(benzylthiomethyl)-N-(3,5-dichloropyridin-4-yl)-4-methoxybenzamide;

N-(3,5-dichloropyridin-4-yl)-3-[3-(pyridin-2-yl)-1,2,4-oxadiazol-5-ylmethoxy]-4-methoxybenzamide;

4-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-ylmethoxy]-N-(3,5-dichloropyridin-4-yl)-5-methoxypyridine-2-carboxamide;

N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(pyridin-2-yloxymethyl)benzamide;

3-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-ylmethoxy]-N-(3,5-dichloro-pyridin-4-yl)-4-methoxybenzamide;

N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(3-methyl-1,2,4-oxadiazol-5-ylmethoxy)benzamide;

N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[2-(pyridin-4-yl)ethoxy]benzamide;

N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-{4-methylthiazol-5-yl}ethoxy)benzamide;

N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-thien-2-ylethoxy)benzamide;

N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-benzyloxybenzamide;

N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(4-phenylbutoxy)benzamide;

N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[2-(pyridin-3-yl)propyloxy]benzamide;

N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-benzyloxyethoxy)benzamide;

3-{2-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]ethyl}-N-(3,5-dichloropyridin-4-yl)-4-methoxybenzamide;

N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(2-phenylethoxy)benzamide;

N-(3,5-dichloropyridin-4-yl)-4-difluoromethoxy-3-(2-phenylethoxy)benzamide;
N-(3,5-dichloropyridin-4-yl)-5-methoxy-4-[2-(4-methoxyphenyl)ethoxy]pyridine-2-carboxamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[2-(pyridin-2-yl)ethoxy]benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[2-(pyridin-3-yl)ethoxy]benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-phenylethyl)benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-phenylethynyl)benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(phenoxymethyl)benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(benzyloxymethyl)benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(4-methoxyphenyl)benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[3-(2-thienyl)-1,2,4-oxadiazol-5-yl]methoxybenzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[2-(4-chlorophenyl)-1,3,4-oxadiazol-5-yl]methoxybenzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]methoxybenzamide;
3-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-N-(3,5-dichloropyridin-4-yl)-4-methoxybenzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(3-phenyl-1,2,4-oxadiazol-5-yl)benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl]benzamide;
N-(3,5-dichloropyridin-4-yl)-5-methoxy-4-(2-[pyridin-3-yl]ethoxy)pyridine-2-carboxamide;

N-(3,5-dichloropyridin-4-yl)-5-methoxy-4-(2-[pyridin-2-yl]ethoxy)pyridine-2-carboxamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-[3-(pyridin-4-yl)propyloxy]benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-[3-(pyridin-3-yl)propyloxy]benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-[2-(4-methoxyphenyl)ethenyl]benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-[2-(pyridin-2-yl)ethynyl]benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-[2-(pyridin-2-yl)ethyl]benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(2-naphthyl)benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(2-benzofuranyl)benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(1-naphthyl)benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(3-thienyl)benzamide;
2-(3,5-dichloropyridin-4-yl)-1-{4-methoxy-3-[2-(pyridin-2-yl)ethoxy]phenyl}ethanone;
2-(3,5-dichloropyridin-4-yl)-1-{4-methoxy-3-[2-(pyridin-3-yl)ethoxy]phenyl}ethanone;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(4-methoxybenzyl)benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(3-(4-methoxyphenyl)propyl)benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(4-methoxyphenylthiomethyl)benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(pyridin-2-ylmethoxy)benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(pyridin-3-ylmethoxy)benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(pyridin-4-ylmethoxy)benzamide;

N-(3,5-dichloro-pyridin-4-yl)-4-methyl-3-(pyridin-2-ylethoxy)benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-{2-(1-piperidinyl)ethoxy}benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-{2-(2-oxo-pyrrolidin-1-yl)ethoxy}benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-phenoxyethoxy)benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-{2-(3-methylpyridin-2-yl)ethoxy}benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-furyl)benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-indanyloxy)benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-{2-(2-furyl)ethoxy}benzamide;
N-(3,5-dichloropyridin-4-yl)-3-{2-(pyridin-2-yl)ethyl}benzamide;
(3,5-dichloropyridin-4-yl)-N-[fluoro(3-{3-(4-chlorophenyl)-1,2,4-oxadiazol-5-ylmethoxy}-4-methoxyphenyl)methylene]amine;
(3,5-dichloropyridin-4-yl)-N-[fluoro(4-methoxy-3-(3-methyl-1,2,4-oxadiazol-5-ylmethoxy)phenyl)methylene]amine;
(3,5-dichloropyridin-4-yl)-N-[fluoro-(4-methoxy-3-{2-pyridin-4-ylethoxy}phenyl)-methylene]amine;
(3,5-dichloropyridin-4-yl)-N-[fluoro(4-methoxy-3-{2-(4-methylthiazol-5-yl)ethoxy}phenyl)methylene]amine;
(3,5-dichloropyridin-4-yl)-N-[fluoro-(4-methoxy-3-{2-thien-2-ylethoxy}phenyl)-methylene]amine;
(3,5-dichloropyridin-4-yl)-N-[fluoro-(4-methoxy-3-{benzyloxy}phenyl)-methylene]amine;
(3,5-dichloropyridin-4-yl)-N-[fluoro-(4-methoxy-3-{4-phenylbutoxy}phenyl)-methylene]amine;
(3,5-dichloropyridin-4-yl)-N-[fluoro-(4-methoxy-3-{(3-pyridin-3-yl)propyloxy}phenyl)-methylene]amine;
(3,5-dichloropyridin-4-yl)-N-[fluoro-(4-methoxy-3-{2-benzyloxyethoxy}phenyl)-methylene]amine;

(3,5-dichloropyridin-4-yl)-N-[fluoro-(4-methoxy-3-(2-piperidinylethoxy}phenyl)-methylene]amine;
2-(3,5-dichloro-pyridin-4-yl)-1-(3-(pyridin-2-ylethoxy)-4-methoxyphenyl)-1-fluoroethane;
and N-oxides, and pharmaceutically acceptable salts and solvates (e.g. hydrates) thereof.

Preferred compounds include:-
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-phenylethoxy)benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(4-phenylbutoxy)benzamide;
N-(3,5-dichloropyridin-4-yl)-4-difluoromethoxy-3-[2-phenylethoxy]benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-benzyloxyethoxy)benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-phenoxyethoxy)benzamide;
N-(3,5-dichloropyridin-4-yl)-5-methoxy-4-[2-(4-methoxyphenyl)ethoxy]pyridine-2-carboxamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-indanyloxy)benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-[2-(pyridin-2-yl)ethoxy]benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-[3-(pyridin-4-yl)propyloxy]benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-[3-(pyridin-3-yl)propyloxy]benzamide;
N-(3,5-dichloropyridin-4-yl)-5-methoxy-4-[2-(pyridin-2-yl)ethoxy]pyridine-2-carboxamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-thien-2-ylethoxy)benzamide;
3-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-ylmethoxy]-N-(3,5-dichloropyridin-4-yl)-4-methoxybenzamide;

3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-ylmethoxy]-N-(3,5-dichloropyridin-4-yl)-4-methoxybenzamide;
N-(3,5-dichloro-pyridin-4-yl)-3-[3-(pyridin-2-yl)-1,2,4-oxadiazol-5-ylmethoxy]-4-methoxybenzamide;
3-[2-(4-chlorophenyl)-1,3,4-oxadiazol-5-ylmethoxy]-N-(3,5-dichloropyridin-4-yl)-4-methoxybenzamide;
and N-oxides, and pharmaceutically acceptable salts and solvates (e.g. hydrates) thereof.

The compounds of the invention exhibit useful pharmacological activity and accordingly are incorporated into pharmaceutical compositions and used in the treatment of patients suffering from certain medical disorders. The present invention thus provides, according to a further aspect, compounds of the invention and compositions containing compounds of the invention for use in therapy.

Compounds within the scope of the present invention exhibit marked pharmacological activities according to tests described in the literature which tests results are believed to correlate to pharmacological activity in humans and other mammals. Detailed in vitro and in vivo procedures are described hereinafter.

Compounds of the invention are inhibitors of tumor necrosis factor, especially TNF-α. Thus, in a further embodiment, the present invention provides compounds of the invention and compositions containing compounds of the invention for use in the treatment of a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of TNF, especially of TNF-α. For example, compounds of the present invention are useful in joint inflammation, including arthritis, rheumatoid arthritis and other arthritic conditions such as rheumatoid spondylitis and osteoarthritis.

Additionally, the compounds are useful in treatment of sepsis, septic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, asthma and other chronic pulmonary diseases, bone resorption diseases, reperfusion injury, graft vs. host reaction and allograft rejection.

Furthermore, the compounds are useful in the treatment of infections such as viral infections and parasitic infections, for example malaria such as cerebral malaria, fever and myalgias due to infection, HIV, AIDS, cachexia such as cachexia secondary to AIDS or to cancer.

Compounds of the invention are also cyclic AMP phosphodiesterase inhibitors, in particular type IV cyclic AMP phosphodiesterase inhibitors. Thus, in another embodiment of the invention, we provide compounds of the invention and compositions containing compounds of the invention for use in the treatment of a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of cyclic AMP phosphodiesterase, especially type IV cyclic AMP phosphodiesterase. For example, compounds within the present invention are useful as bronchodilators and prophylactic agents useful against asthma, and agents for the inhibition of eosinophil accumulation and of the function of eosinophils, e.g. for the treatment of inflammatory airways disease, especially reversible airway obstruction or asthma, and for the treatment of other diseases and conditions characterized by, or having an etiology involving, morbid eosinophil accumulation. As further examples of conditions which can be ameliorated by the administration of inhibitors of cyclic AMP phosphodiesterase such as compounds of the invention there may be mentioned inflammatory diseases, such as atopic dermatitis, urticaria, allergic rhinitis, psoriasis, rheumatoid arthritis, inflammatory bowel diseases (e.g. Crohn's disease, ulcerative colitis), adult respiratory distress syndrome and

diabetes insipidus, other proliferative skin diseases such as keratosis and various types of dermatitis, conditions associated with cerebral metabolic inhibition, such as cerebral senility, multi-infarct dementia, senile dementia (Alzheimer's disease), and memory impairment associated with Parkinson's disease, and conditions ameliorated by neuroprotectant activity, such as cardiac arrest, stroke, and intermittent claudication.

Other disease states that may be treated with the compounds of the present invention include pyresis, autoimmune diseases (e.g. systemic lupus erythematosus, allergic erythematosus, multiple sclerosis), type I diabetes mellitus, psoriasis, Beçhet's disease, anaphylactoid purpura nephritis, chronic glomerulonephritis, and leukemia.

A special embodiment of the therapeutic methods of the present invention is the treating of asthma.

Another special embodiment of the therapeutic methods of the present invention is the treating of joint inflammation.

According to a further feature of the invention there is provided a method for the treatment of a human or animal patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of cyclic AMP phosphodiesterase or of TNF, especially TNF-α, for example conditions as hereinbefore described, which comprises the administration to the patient of an effective amount of compound of the invention or a composition containing a compound of the invention.

"Effective amount" is meant to describe an amount of compound of the present invention effective in inhibiting cyclic AMP

phosphodiesterase and/or TNF and thus producing the desired therapeutic effect.

According to another aspect of the invention, there is provided the use of a compound of the invention in the manufacture of a medicament for the treatment of a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of cyclic AMP phosphodiesterase, especially type IV cyclic AMP phosphodiesterase.

According to a further aspect of the invention, there is provided the use of a compound of the invention in the manufacture of a medicament for the treatment of a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of TNF, especially of TNF-α.

References herein to treatment should be understood to include prophylactic therapy as well as treatment of established conditions.

The present invention also includes within its scope pharmaceutical compositions comprising at least one of the compounds of the invention in association with a pharmaceutically acceptable carrier or excipient.

Compounds of the invention may be administered by any suitable means. In practice compounds of the present invention may generally be administered parenterally, rectally, by inhalation or, especially, by the oral route.

Compositions according to the invention may be prepared according to the customary methods, using one or more pharmaceutically acceptable adjuvants or excipients. The adjuvants comprise, inter alia, diluents, sterile aqueous media

and the various non-toxic organic solvents. The compositions may be presented in the form of tablets, capsules, pills, granules, powders, aqueous solutions or suspensions, injectable solutions, elixirs or syrups, and can contain one or more agents chosen from the group comprising sweeteners, flavorings, colorings, or stabilizers in order to obtain pharmaceutically acceptable preparations. The choice of vehicle and the content of active substance in the vehicle are generally determined in accordance with the solubility and chemical properties of the active compound, the particular mode of administration and the provisions to be observed in pharmaceutical practice. For example, excipients such as lactose, sodium citrate, calcium carbonate, dicalcium phosphate and disintegrating agents such as starch, alginic acids and certain complex silicates combined with lubricants such as magnesium stearate, sodium lauryl sulphate and talc may be used for preparing tablets. To prepare a capsule, it is advantageous to use lactose and high molecular weight polyethylene glycols. When aqueous suspensions or solutions are used they can contain emulsifying agents or agents which facilitate suspension or solubilisation. Diluents such as sucrose, ethanol, polyethylene glycol, propylene glycol, glycerol and chloroform or mixtures thereof may also be used.

For parenteral administration, emulsions, suspensions or solutions of the products according to the invention in vegetable oil, for example sesame oil, groundnut oil or olive oil, or aqueous-organic solutions such as water and propylene glycol, injectable organic esters such as ethyl oleate, as well as sterile aqueous solutions of the pharmaceutically acceptable salts, are used. The solutions of the salts of the products according to the invention are especially useful for administration by intramuscular or subcutaneous injection. The aqueous solutions, also comprising solutions of the salts in pure distilled water, may be used for intravenous

administration with the proviso that their pH is suitably adjusted, that they are judiciously buffered and rendered isotonic with a sufficient quantity of glucose or sodium chloride and that they are sterilized by heating, irradiation or microfiltration.

For administration by inhalation compounds of the invention may be dissolved or suspended in a suitable carrier for use in a nebulizer or a suspension or solution aerosol, or may be absorbed or adsorbed onto a suitable solid carrier for use in a dry powder inhaler.

Solid compositions for rectal administration include suppositories formulated in accordance with known methods and containing at least one compound of the invention.

The percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. Obviously, several unit dosage forms may be administered at about the same time. The dose employed will be determined by the physician, and depends upon the desired therapeutic effect, the route of administration and the duration of the treatment, and the condition of the patient. In the adult, the doses are generally from about 0.001 to about 50, preferably about 0.001 to about 5, mg/kg body weight per day by inhalation, from about 0.01 to about 100, preferably 0.1 to 70, more especially 0.5 to 10, mg/kg body weight per day by oral administration, and from about 0.001 to about 10, preferably 0.01 to 1, mg/kg body weight per day by intravenous administration. In each particular case, the doses will be determined in accordance with the factors distinctive to the subject to be treated, such as age, weight, general state of health and other characteristics which can influence the efficacy of the medicinal product.

The compounds according to the invention may be administered as frequently as necessary in order to obtain the desired therapeutic effect. Some patients may respond rapidly to a higher or lower dose and may find much weaker maintenance doses adequate. For other patients, it may be necessary to have long-term treatments at the rate of 1 to 4 doses per day, in accordance with the physiological requirements of each particular patient. Generally, the active product may be administered orally 1 to 4 times per day. Of course, for some patients, it will be necessary to prescribe not more than one or two doses per day.

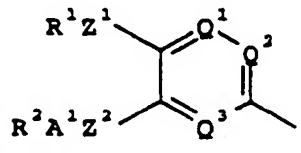
The compounds of the present invention may also be formulated for use in conjunction with other therapeutic agents such as agents which increase cyclic AMP production including β-agonists and PGE_2. It is to be understood that the present invention includes combinations of compounds of the present invention with one or more of the aforementioned therapeutic agents.

Compounds of the invention may be prepared by the application or adaptation of known methods, which means methods used heretofore or described in the literature, for example as illustrated in the Examples and Reference Examples and chemical equivalents thereof. In the reactions described hereinafter it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice, for examples see T.W. Green and P.G.M.Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991.

General formula (I) can also be written as:-

$$T^1\text{-}Z^3R^3 \qquad (I)$$

wherein Z^3 and R^3 are as hereinbefore defined and T^1 represents a group of the general formula:-



T^1

wherein the symbols are as hereinbefore defined.

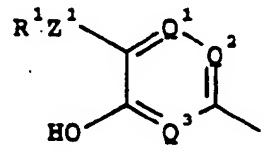
According to a further feature of the invention, in a process (A), compounds of formula (I) wherein T^1 is as hereinbefore defined, Z^3 represents a -CO-NH- linkage and R^3 are as hereinbefore defined, and preferably represents a heteroaryl group containing at least one nitrogen atom, particularly a substituted heteroaryl group containing at least one nitrogen atom wherein the substitution is such that the pKa of the said nitrogen atom is about 10 or less, e.g. a 3,5-dichloropyrid-4-yl group, may be prepared by the reaction of compounds of the general formula (I) wherein T^1 and R^3 are as immediately hereinbefore defined, and Z^3 represents a -C(F)=N- linkage, with a suitable base, for example potassium trimethylsilanolate. The reaction is optionally carried out in an inert solvent, for example an ether, such as tetrahydrofuran, preferably at a temperature from about 0°C to the reflux temperature.

Compounds of formula (I) wherein T^1 is as hereinbefore defined (but where Z^2 represents oxygen), Z^3 represents a -C(F)=N-

linkage and R^3 is as hereinbefore defined, may be prepared from compounds of the general formula (II):-

$$T^2\text{-}CF{=}NR^3 \qquad (II)$$

wherein R^3 are as hereinbefore defined and T^2 represents a group of the general formula:-



T^2

wherein R^1, Q^1, Q^2, Q^3 and Z^1 are as hereinbefore defined, by reaction with alcohols of formula (III):-

$$R^2A^1OH \qquad (III)$$

wherein R^2 and A^1 are as hereinbefore defined and A^1 represents an alkylene linkage, in the presence of a triarylphosphine, such as triphenylphosphine, and a dialkyl ester, such as the diisopropyl or diethyl ester of azodicarboxylic acid. The reaction preferably takes place in an inert solvent, such as tetrahydrofuran, preferably at a temperature from about 0°C to about 60°C.

According to a further feature of the invention, in a process (B), compounds of formula (I) wherein T^1 and R^3 are as hereinbefore defined and Z^3 represents a -CO-NH- linkage may be prepared by the reaction of compounds of the general formula (IV):-

$$T^1\text{-}COX^4 \qquad (IV)$$

wherein T^1 is as hereinbefore defined and X^4 represents an azido group or a halogen, e.g. bromine or, preferably, chlorine atom, with compounds of the general formula (V):-

$$R^3NHR^4 \qquad (V)$$

wherein R^3 is as hereinbefore described, including N-oxides of heteroaryl groups, and R^4 represents a hydrogen atom or an alkanoyl, e.g. acetyl group. The reaction may be carried out in the presence of an amine, preferably a tertiary amine, e.g. triethylamine or pyridine, optionally in an inert solvent, for example a halogenated hydrocarbon such as dichloromethane, dimethylformamide, or an ether (e.g. diethyl ether or tetrahydrofuran), preferably at a temperature from 0°C to the reflux temperature or at the melting point of the reaction mixture. Alternatively, the reaction may be carried out in the presence of a base such as an alkali metal hydride, e.g. sodium hydride, optionally in an inert solvent, for example a halogenated hydrocarbon such as dichloromethane, dimethylformamide, or an ether (e.g. diethyl ether or tetrahydrofuran), preferably at a temperature from 0°C to the reflux temperature or at the melting point of the reaction mixture, and this method is preferred when R^3 represents a heteroaryl group containing at least one nitrogen atom, preferably a substituted heteroaryl group containing at least one nitrogen atom wherein the substitution is such that the pKa of the said nitrogen atom is about 10 or less, e.g. a 3,5-dichloropyrid-4-yl group.

According to a further feature of the invention, in a process (C), compounds of formula (I) wherein T^1 and R^3 are as hereinbefore defined and Z^3 represents a $-CO-CH_2-$ linkage may

be prepared by reaction of compounds of the general formula (VI):-

$$T^1\text{-}COOR^5 \qquad (VI)$$

wherein T^1 is as hereinbefore defined and R^5 represents an alkyl group with compounds of the general formula (VII):-

$$R^3\text{-}CH_3 \qquad (VII)$$

wherein R^3 is as hereinbefore defined, in the presence of a strong base such as lithium diisopropylamide (usually prepared in situ from butyl lithium and diisopropylamine), in an inert solvent, for example an ether, e.g. tetrahydrofuran, preferably at a temperature from -65°C to 0°C.

According to a further feature of the invention, in a process (D), compounds of formula (I) wherein T^1 and R^3 are as hereinbefore defined and Z^3 represents a $-CO-CH_2-$ linkage may be prepared by the oxidation of compounds of the general formula (VIII):-

$$T^1\text{-}CH(OH)CH_2R^3 \qquad (VIII)$$

wherein T^1 and R^3 are as hereinbefore defined, by the application or adaptation of known methods. The oxidation can be carried out, for example, by reaction with oxalyl chloride and dimethyl sulphoxide, in a solvent such as dichloromethane, and preferably at a temperature lower than -65°C. These conditions are especially convenient for the preparation of compounds wherein Z^1 and Z^2 each represents an oxygen atom.

According to a further feature of the invention, compounds of formula (I), wherein T^1 and R^3 are as hereinbefore defined and Z^3 represents a $-CZ-CH_2-$ linkage, and preferably Z represents an oxygen atom, may be prepared by the reaction of compounds of the general formula (IX):-

$$T^1-CZNR^6OR^7 \qquad (IX)$$

wherein T^1 and Z are as hereinbefore defined and R^6 and R^7 represent C_{1-4}alkyl, e.g. methyl, groups, with compounds of formula (VII) wherein R^3 is as hereinbefore defined, in the presence of a strong base such as lithium diisopropylamide (usually prepared in situ from butyl lithium and diisopropylamine), preferably at a low temperature.

According to a further feature of the invention, compounds of formula (I) wherein T^1 and R^3 are as hereinbefore defined and Z^3 represents a $-CO-CH_2-$ linkage may be prepared by the reaction of compounds of the general formula (X):-

$$T^1-CN \qquad (X)$$

wherein T^1 is as hereinbefore defined, with Grignard reagents which may be represented by the general formula (XI):-

$$R^3MgX^5 \qquad (XI)$$

wherein R^3 is as hereinbefore defined and X^5 represents a halogen, preferably a bromine atom.

According to a further feature of the invention, compounds of formula (I) wherein T^1 and R^3 are as hereinbefore defined and Z^3 represents a $-CZ-NH-$ linkage, more especially those wherein

Z and Z^1 represent oxygen, may be prepared by the reaction of compounds of the general formula (XII):-

$$T^1\text{-}CZNH_2 \qquad (XII)$$

wherein T^1 and Z are as hereinbefore defined and Z preferably represents oxygen, with compounds of the general formula (XIII):-

$$R^3X^6 \qquad (XIII)$$

wherein R^3 is as hereinbefore defined and X^6 represents a halogen, preferably a chlorine atom. Preferably the reaction takes place in the presence of a base, for example an alkali metal hydride, e.g. sodium hydride, an alkali metal alkoxide, e.g. potassium t-butoxide, an alkali metal hydroxide, e.g. sodium hydroxide or an alkali metal carbonate, e.g. sodium carbonate, or an amine, preferably a tertiary amine, e.g. triethylamine or pyridine, optionally in an inert solvent, for example dichloromethane, dimethylformamide, or an ether, e.g. diethyl ether or tetrahydrofuran, preferably at a temperature from 0°C to the reflux temperature.

According to a further feature of the invention, compounds of formula (I) wherein T^1 and R^3 are as hereinbefore defined and Z^3 represents an $-O-CH_2-$ linkage may be prepared by the reaction of compounds of the general formula (XIV):-

$$T^1\text{-}OH \qquad (XIV)$$

wherein T^1 is as hereinbefore defined, with compounds of the general formula (XV):-

$R^3CH_2X^7$ (XV)

wherein R^3 is as hereinbefore defined and X^7 represents a halogen atom, especially a chlorine atom, preferably in the presence of a base such as an alkali metal carbonate, e.g. potassium carbonate, preferably in a solvent such as dimethylformamide.

According to a further feature of the present invention, compounds of formula (I) wherein T^1 and R^3 are as hereinbefore defined and Z^3 represents a -O-CO- linkage may be prepared by the reaction of compounds of formula (XIV) wherein T^1 is as hereinbefore defined, with compounds of the general formula (XVI):-

R^3COX^8 (XVI)

wherein R^3 is as hereinbefore defined, and X^8 represents a halogen, preferably a chlorine atom, preferably in the presence of a base such as a tertiary amine, e.g. triethylamine, preferably in a solvent such as dichloromethane.

According to a further feature of the present invention, compounds of formula (I) wherein T^1 and R^3 are as hereinbefore defined and Z^3 represents a -NH-CO- linkage may be prepared by the reaction of the general formula (XVII):-

T^1-NH_2 (XVII)

wherein T^1 is are as hereinbefore defined, with compounds of formula (XVI) wherein R^3 and X^8 are as hereinbefore defined, preferably in the presence of a base such as a tertiary amine,

e.g. triethylamine, preferably in a solvent such as dichloromethane.

According to a further feature of the present invention, compounds of formula (I) wherein T^1 and R^3 are as hereinbefore defined and Z^3 represents a -NH-CO-NH- linkage may be prepared by the reaction of compounds of formula (XVII) wherein T^1 is as hereinbefore defined with compounds of the general formula (XVIII):-

$$R^3NCO \qquad (XVIII)$$

wherein R^3 is as hereinbefore defined, preferably in the presence of a base such as a tertiary amine, e.g. triethylamine, preferably in a solvent such as dichloromethane.

According to a further feature of the present invention, compounds of formula (I) wherein T^1 and R^3 are as hereinbefore defined and Z^3 represents a -NH-CO-NH- linkage may be prepared by the reaction of compounds of formula (XVII) wherein T^1 is as hereinbefore defined with compounds of formula (V) wherein R^3 is as hereinbefore defined and R^4 represents a hydrogen atom, together with phosgene or a source thereof. The reaction is preferably carried out by reacting the compound of formula (XVII) with phosgene or, preferably, bis(trichloromethyl) carbonate, and by then reacting the product of that reaction with the cation derived from the compound of formula (V), for example by reaction with a base such as sodium hydride. The reactions are preferably carried out in suitable solvents such as dichloromethane and tetrahydrofuran.

According to a further feature of the present invention, compounds of formula (I) wherein T^1 and R^3 are as hereinbefore

defined and Z^3 represents a $-CH_2-NH-$ linkage may be prepared by the reaction of compounds of the general formula (XIX):-

$$T^1-CHO \qquad (XIX)$$

wherein T^1 is as hereinbefore defined, with compounds of formula (V) wherein R^3 is as hereinbefore defined and R^4 represents a hydrogen atom, followed by reduction with a compound such as sodium cyanoborohydride. This reaction is especially suitable for the preparation of compounds wherein R^3 represents an optionally substituted phenyl or naphthyl group.

According to a further feature of the present invention, compounds of formula (I) wherein T^1 and R^3 are as hereinbefore defined and Z^3 represents a $-CH_2-NH-$ linkage may be prepared by the reaction of compounds of the general formula (XX):-

$$T^1-CH_2X^9 \qquad (XX)$$

wherein T^1 is as hereinbefore defined and X^9 represents a halogen, preferably bromine, atom with compounds of formula (V) wherein R^3 is as hereinbefore defined and R^4 represents a hydrogen atom. The reaction preferably takes place in the presence of a base such as sodium hydride. The reaction is especially suitable for the preparation of compounds wherein R^3 represents an optionally substituted heteroaryl group.

According to a further feature of the present invention, compounds of formula (I) wherein T^1 and R^3 are as hereinbefore defined Z^2 represents an oxygen atom, and Z^3 represents a $-SO_2-NH-$ linkage may be prepared by the reaction of compounds of the general formula (XXI):-

$$T^2\text{-}SO_2NHR^3 \qquad (XXI)$$

wherein R^3 and T^2 are as hereinbefore defined, with compounds of the general formula (XXII):-

$$R^2A^1X^{10} \qquad (XXII)$$

wherein R^2 and A^1 are as hereinbefore defined and X^{10} represents a halogen, preferably bromine, atom or an alkylsulphonyl or arylsulphonyl, e.g. p-toluene-sulphonyl, group, preferably after treatment with a base such as sodium hydride, preferably in a solvent such as dimethylformamide.

According to a further feature of the present invention, compounds of formula (I) wherein T^1 and R^3 are as hereinbefore defined and Z^3 represents a $-S-CH_2-$ linkage may be prepared by the reaction of compounds of the general formula (XXIII):-

$$T^1\text{-}SH \qquad (XXIII)$$

wherein T^1 is as hereinbefore defined, with compounds of formula (XV) wherein R^3 and X^7 are as hereinbefore defined, and preferably X^7 represents a bromine atom, preferably after reaction with a base such as an alkali metal alkoxide, e.g. sodium methoxide.

According to a further feature of the present invention, compounds of formula (I) wherein T^1 and R^3 are as hereinbefore defined and Z^3 represents a $-CF_2-O-$ linkage may be prepared by the reaction of compounds of the general formula (XXIV):-

T^1-CF_2Br (XXIV)

wherein T^1 is as hereinbefore defined, with compounds of the general formula (XXV):-

R^3OH (XXV)

wherein R^3 is as hereinbefore defined, preferably with the aid of a base such as sodium hydride, preferably in a solvent such as dimethylformamide.

According to a further feature of the present invention, compounds of formula (I) wherein T^1 and R^3 are as hereinbefore defined and Z^3 represents a -NH-CO-O- linkage may be prepared by the reaction of compounds of the general formula (XXVI):-

T^1-NCO (XXVI)

wherein T^1 is as hereinbefore defined, with compounds of formula (XXV) wherein R^3 is as hereinbefore defined, preferably with the aid of a base such as a tertiary amine, e.g. triethylamine, preferably in a solvent such as dichloromethane.

According to a further feature of the present invention, compounds of formula (I) wherein T^1 and R^3 are as hereinbefore defined and Z^3 represents a $-NH-CH_2-$ linkage may be prepared by the reaction of compounds of formula (XVII) wherein T^1 is as hereinbefore defined, with compounds of the general formula (XXVII):-

R^3CHO (XXVII)

wherein R^3 is as hereinbefore defined, preferably with the aid of a reducing agent such as sodium cyanoborohydride.

According to a further feature of the present invention, compounds of formula (I) wherein T^1 and R^3 are as hereinbefore defined and Z^3 represents a $-NH-SO_2-$ linkage may be prepared by the reaction of compounds of formula (XVII, T^1-NH_2) wherein T^1 is as hereinbefore defined with compounds of the general formula (XXVIII):-

$$R^3SO_2X^{11} \qquad \text{(XXVIII)}$$

wherein R^3 is as hereinbefore defined and X^{11} represents a halogen, preferably chlorine, atom, preferably with the aid of a base such as a tertiary amine, e.g. triethylamine, preferably in a solvent such as tetrahydrofuran.

According to a further feature of the present invention, compounds of formula (I) wherein T^1 and R^3 are as hereinbefore defined and Z^3 represents a $-O-CO-NH-$ linkage may be prepared by the reaction of compounds of formula (XIII, T^1-OH) wherein T^1 is as hereinbefore defined with compounds of formula (XVIII, R^3NCO) wherein R^3 is as hereinbefore defined, or with compounds of formula (V) wherein R^3 is as hereinbefore defined and R^4 represents a hydrogen atom, together with phosgene or a source thereof, preferably, bis(trichloromethyl)carbonate, preferably with the aid of a base such as a tertiary amine, e.g. triethylamine, preferably in a solvent such as dichloromethane.

According to a further feature of the present invention, compounds of formula (I) wherein T^1 and R^3 are as hereinbefore defined and Z^3 represents a $-O-CF_2-$ linkage may be prepared by

the reaction of compounds of formula (XIV, T^1-OH) wherein T^1 is as hereinbefore defined with compounds of the general formula (XXIX):-

$$R^3CF_2Br \qquad (XXIX)$$

wherein R^3 is as hereinbefore defined, preferably with the aid of a base such as sodium hydride, preferably in a solvent such as dimethylformamide.

According to a further feature of the present invention, compounds of formula (I) wherein T^1 and R^3 are as hereinbefore defined and Z^3 represents an ethynyl linkage may be prepared by the reaction of compounds of the general formula (XXX):-

$$T^1\text{-}I \qquad (XXX)$$

wherein T^1 is as hereinbefore defined, with acetylenes of the general formula (XXXI):-

$$R^3C{\equiv}CH \qquad (XXXI)$$

wherein R^3 is as hereinbefore defined. Preferably the reaction is carried out with the aid of a catalyst, e.g. palladium on carbon and cuprous iodide, preferably with the aid of a base such as a tertiary amine, e.g. triethylamine, preferably in a solvent such as dimethylformamide.

According to a further feature of the present invention, compounds of formula (I) wherein T^1 and R^3 are as hereinbefore defined and Z^3 represents a $-CH_2-O-$ linkage may be prepared by the reaction of compounds of the general formula (XXXII):-

T^1-CH_2OH (XXXII)

wherein T^1 is as hereinbefore defined, with compounds of formula (XIII) wherein R^3 and X^6 are as hereinbefore defined, preferably with the aid of a base such as an alkali metal alkoxide, e.g. potassium t-butoxide. The reaction is preferably carried out in a solvent such as tetrahydrofuran.

According to a further feature of the present invention, compounds of formula (I) wherein T^1 and R^3 are as hereinbefore defined and Z^3 represents a $-CH_2-O-$ linkage may be prepared by the reaction of compounds of formula (XX) wherein T^1 and X^9 are as hereinbefore defined with compounds of formula (XXV) wherein R^3 is as hereinbefore defined, preferably with the aid of a base such as an alkali metal alkoxide, e.g. potassium t-butoxide.

According to a further feature of the present invention, compounds of formula (I) wherein T^1 and R^3 are as hereinbefore defined and Z^3 represents a -CO-CO-NH- linkage may be prepared by the reaction of compounds of the general formula (XXXIII):-

T^1-COCOOH (XXXIII)

wherein T^1 is as hereinbefore defined, with dichloromethyl methyl ether in dichloromethane, followed by reaction with compounds of formula (V) wherein R^3 is as hereinbefore defined and R^4 represents a hydrogen atom, preferably with the aid of a base such as sodium hydride, preferably in a solvent such as tetrahydrofuran.

According to a further feature of the present invention, compounds of formula (I) wherein T^1 and R^3 are as hereinbefore

defined and Z^3 represents a -CO-CO- linkage may be prepared by the oxidation of compounds of formula (VIII) wherein T^1 and R^3 are as hereinbefore defined, for example by reaction with pyridinium dichromate, preferably in a solvent such as dichloromethane. This reaction is particularly suitable for the preparation of compounds wherein R^3 represents a heteroaryl, for example an optionally substituted pyridyl, group.

According to a further feature of the present invention, compounds of formula (I) wherein T^1 and R^3 are as hereinbefore defined and Z^3 represents a trans -N=N- linkage may be prepared by the reaction of compounds of the general formula (XXXIV):-

$$T^1\text{-}N_2^+ \ BF_4^- \qquad \text{(XXXIV)}$$

wherein T^1 is as hereinbefore defined, with compounds of the general formula (XXXV):-

$$R^3H \qquad \text{(XXXV)}$$

wherein R^3 is as hereinbefore defined, preferably with the aid of a base such as lithium diisopropylamide.

According to a further feature of the present invention, compounds of formula (I) wherein T^1 and R^3 are as hereinbefore defined and Z^3 represents a $-CH_2-S-$ linkage may be prepared by the reaction of compounds of formula (XX) wherein T^1 and X^9 are as hereinbefore defined with compounds of the general formula (XXXVI):-

$$R^3\text{-}SH \qquad \text{(XXXVI)}$$

wherein R^3 is as hereinbefore defined, preferably with the aid of a base such as an alkali metal carbonate, e.g. potassium carbonate.

According to a further feature of the present invention, compounds of formula (I) wherein T^1 and R^3 are as hereinbefore defined and Z^3 represents a $-CH_2-CO-$ linkage may be prepared by the oxidation of compounds of the general formula (XXXVII):-

$$T^1-CH_2-CH(OH)-R^3 \qquad (XXXVII)$$

wherein T^1 and R^3 are as hereinbefore defined. The oxidation may conveniently be carried out, for example, by reaction with oxalyl chloride and dimethyl sulphoxide, in a solvent such as dichloromethane, and preferably at a temperature lower than -65°C. Alternatively, the oxidation may be carried out by reaction with chromium trioxide in the presence of 3,5-dimethylpyrazole.

According to a further feature of the present invention, compounds of formula (I) wherein T^1 and R^3 are as hereinbefore defined and Z^3 represents a $-C(=NOR^C)-CH_2-$ linkage (where R^C is as hereinbefore described) may be prepared by reaction of compounds of (I) wherein T^1 and R^3 are as hereinbefore defined and Z^3 represents a $-CO-CH_2-$ linkage, with a N-alkyl- or N-arylalkyl-hydroxylamine in the presence of pyridine.

According to a further feature of the present invention, compounds of formula (I) wherein T^1 and R^3 are as hereinbefore defined and Z^3 represents a $-CH(F)-CH_2-$ linkage may be prepared by reaction of compounds of the general formula (VIII), wherein T^1 and R^3 are as hereinbefore defined, with diethylaminosulphur

trifluoride in an inert solvent, such as dichloromethane, and at a temperature at about room temperature.

According to a further feature of the present invention, in a process (E) compounds of the invention may be prepared by interconversion of other compounds of the invention.

Thus, for example, compounds of the invention containing a heterocyclic group wherein the hetero atom is a nitrogen atom may be oxidised to the corresponding N-oxides. This interconversion is especially convenient for the preparation of compounds of the invention wherein Z^1 and Z^2 both represent oxygen atoms and wherein the linkage A^1 contains no oxidizable groups containing sulphur. The oxidation may conveniently be carried out by means of reaction with a mixture of hydrogen peroxide and an organic acid, e.g. acetic acid, preferably at or above room temperature, for example at a temperature of about 60-90°C. Alternatively, the oxidation may be carried out by reaction with a peracid, for example m-chloroperoxybenzoic acid, in an inert solvent such as dichloromethane, at a temperature from about room temperature to reflux, preferably at elevated temperature. The oxidation may alternatively be carried out by reaction with hydrogen peroxide in the presence of sodium tungstate at temperatures between room temperature and about 60°C. This last method is preferred for compounds containing an acid-labile group.

As another example of the interconversion process, an N-oxide group within a compound of formula (I) may be reduced to a nitrogen atom. More particularly, one of the N-oxide groups in a compound of formula (I) wherein Q^1, Q^2 or Q^3 represents a nitrogen atom in its oxidised form and R^2 and/or R^3 represents a heteroaryl group containing one or more nitrogen ring atoms

in its oxidised form, may be reduced to a nitrogen atom. Indeed, the N-oxide group in the group R^2 and/or R^3 in such a compound can be reduced to a nitrogen leaving the other N-oxide group unchanged.

The reduction of an N-oxide group may be carried out by reaction with diphosphorus tetraiodide in an inert solvent, such as dichloromethane, preferably at or near room temperature, or by reaction with a chlorotrialkylsilane, preferably chlorotrimethylsilane, in the presence of zinc and an alkali metal iodide, e.g. potassium iodide, in an inert solvent, e.g. acetonitrile, at a temperature between about 0°C and about room temperature, preferably below room temperature.

According to a further example of the interconversion process, compounds of the invention containing hydroxy moieties may be converted to their esters by the application or adaptation of known methods of esterification. For example, the appropriate acid may be converted to an acid halide, e.g. by reaction with thionyl chloride or oxalyl chloride, and then the acid halide may be reacted with the appropriate alcohol of formula (I), preferably in the presence of a base, for example a tertiary amine, e.g. triethylamine.
Alternatively, the appropriate alcohol of formula (I) may be reacted with the appropriate acid in the presence of compounds such as diisopropyl azodicarboxylate and triphenylphosphine, preferably in a dry ethereal solvent, e.g. diethyl ether or tetrahydrofuran, preferably at or near room temperature.

As another example of the interconversion process, compounds of the invention containing hydroxy moieties may be prepared by hydrolysis of corresponding esters of the invention. The hydrolysis may conveniently be carried out by alkaline hydrolysis using a base, such as an alkali metal hydroxide or carbonate, in the presence of an aqueous/organic solvent

mixture, using organic solvents such as dioxan, tetrahydrofuran or methanol, at a temperature from about ambient to about reflux. The hydrolysis of the esters may also be carried out by acid hydrolysis using an inorganic acid, such as hydrochloric acid, in the presence of an aqueous/inert organic solvent mixture, using organic solvents such as dioxan or tetrahydrofuran, at a temperature from about 50°C to about 80°C. Such hydrolytic means are particularly suitable for preparing compounds of the invention in which Z^3 represents a ketomethylene linkage.

As another example of the interconversion process, compounds of formula (I) wherein R^2 and/or R^3 represents or contain an aryl group which is substituted by a formyl group may be prepared by oxidising the corresponding compounds of formula (I) wherein R^2 and/or R^3 represents or contain an aryl group which is substituted by a hydroxymethyl group for example with oxalyl chloride and dimethyl sulphoxide, in a solvent such as dichloromethane, and preferably at a temperature lower than about -65°C, or, preferably, by reaction with a complex of sulphur trioxide with an amine such as pyridine, preferably in the presence of an amine such as triethylamine, preferably at about room temperature.

As another example of the interconversion process, compounds of formula (I) wherein R^2 and/or R^3 represents or contain an aryl group which is substituted by an amino group may be prepared by reducing the corresponding compounds of formula (I) wherein R^2 and/or R^3 represents or contains an aryl group which is substituted by a nitro group, preferably with iron in acidic conditions, such as in acetic acid, preferably at or above room temperature, more especially at the reflux temperature. Alternatively the reduction may be carried out by reaction with hydrazine hydrate in the presence of ferric

chloride and activated carbon, conveniently in a solvent such as methanol, at temperatures from about 25°C to about 80°C.

As another example of the interconversion process, compounds of formula (I) wherein R^2 and/or R^3 represents or contains an aryl group which is substituted by an acylamino or aroylamino group may be prepared from compounds of formula (I) wherein R^2 and/or R^3 represents or contains an aryl group which is substituted by an amino group, preferably by means of reaction with the appropriate acid halide or acid anhydride in the presence of a tertiary base, such as triethylamine, optionally in an inert solvent, and preferably at a temperature from about 0°C to reflux.

As another example of the interconversion process, compounds of formula (I) wherein R^2 and/or R^3 represents or contains an aryl group which is substituted by a carboxamido group may be prepared from compounds of formula (I) wherein R^2 and/or R^3 represents or contains an aryl group which is substituted by a cyano group, by means of reaction with hydrogen peroxide and potassium carbonate in dimethyl sulphoxide.

As another example of the interconversion process, compounds of formula (I) wherein R^2 and/or R^3 represents or contains an aryl group which is substituted by a cyano group may be prepared from compounds of formula (I) wherein R^2 and/or R^3 represents or contains an aryl group which is substituted by a bromine atom, by means of reaction with zinc cyanide in the presence of tetrakis(triphenylphosphine) palladium(0) in an inert solvent, such as dimethylformamide, at a temperature at about 100°C.

As another example of the interconversion process, compounds of formula (I) wherein Z^3 represents a cis -N=N- linkage may be prepared by the action of ultraviolet radiation upon their trans-isomers.

As another example of the interconversion process, compounds of formula (I) containing sulphoxide linkages may be prepared by the oxidation of corresponding compounds containing -S- linkages. For example, the oxidation may conveniently be carried out by means of reaction with a peroxyacid, e.g. 3-chloroperbenzoic acid, preferably in an inert solvent, e.g. dichloromethane, preferably at or near room temperature, or alternatively by means of potassium hydrogen peroxomonosulphate in a medium such as aqueous methanol, buffered to about pH5, at temperatures between about 0°C and room temperature. This latter method is preferred for compounds containing an acid-labile group.

As another example of the interconversion process, compounds of formula (I) containing sulphone linkages may be prepared by the oxidation of corresponding compounds containing -S- or sulphoxide linkages. For example, the oxidation may conveniently be carried out by means of reaction with a peroxyacid, e.g. 3-chloroperbenzoic acid, preferably in an inert solvent, e.g. dichloromethane, preferably at or near room temperature, or alternatively the oxidation can be carried out by means of sodium metaperiodate in a medium such as aqueous methanol.

As another example of the interconversion process, compounds of formula (I) wherein Z^3 represents a $-CS-CH_2-$ linkage may be prepared from compounds of formula (I) wherein Z^3 represents a $-CO-CH_2-$ linkage by reaction with phosphorus pentasulphide or 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-

disulphide, preferably in a solvent such as pyridine or toluene, and preferably at a temperature from 0°C to the reflux temperature.

As another example of the interconversion process, compounds of formula (I) containing a hydroxymethyl group may be prepared by the reduction of the corresponding compounds of formula (I) containing an aryloxycarbonyl or, particularly, alkoxycarbonyl group, preferably by means of reaction with an alkali metal borohydride, preferably in an inert solvent, e.g. tetrahydrofuran, and preferably at or near room temperature.

As another example of the interconversion process, compounds of formula (I) wherein R^1 is as hereinbefore defined and is substituted on its α-carbon atom by fluorine and Z^1 is sulphur may be prepared by the reaction of xenon difluoride with corresponding compounds of formula (I) wherein said α-carbon atoms carry hydrogen atoms instead of said fluorine atoms. The reaction may be conveniently carried out in a solvent, such as dichloromethane, in the presence of a molecular sieve, and in an inert atmosphere, at a low temperature, e.g. at or near 0°C. This method is especially convenient for the conversion of compounds wherein R^1 represents a methyl group to compounds wherein R^1 represents a difluoromethyl group.

According to a further feature of the invention, acid addition salts of the compounds of this invention may be prepared by reaction of the free base with the appropriate acid, by the application or adaptation of known methods. For example, the acid addition salts of the compounds of this invention may be prepared either by dissolving the free base in water or aqueous alcohol solution or other suitable solvents containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and acid in an organic

solvent, in which case the salt separates directly or can be obtained by concentration of the solution.

The acid addition salts of the compounds of this invention can be regenerated from the salts by the application or adaptation of known methods. For example, parent compounds of the invention can be regenerated from their acid addition salts by treatment with an alkali, e.g. aqueous sodium bicarbonate solution or aqueous ammonia solution.

It will be appreciated that compounds of the present invention may contain asymmetric centres. These asymmetric centres may independently be in either the R or S configuration. It will be apparent to those skilled in the art that certain compounds of the invention may also exhibit geometrical isomerism. It is to be understood that the present invention includes individual geometrical isomers and stereoisomers and mixtures thereof, including racemic mixtures, of compounds of formula (I) hereinabove. Such isomers can be separated from their mixtures, by the application or adaptation of known methods, for example chromatographic techniques and recrystallization techniques, or they are separately prepared from the appropriate isomers of their intermediates.

The starting materials and intermediates may be prepared by the application or adaptation of known methods, for example methods as described in the Reference Examples or their obvious chemical equivalents.

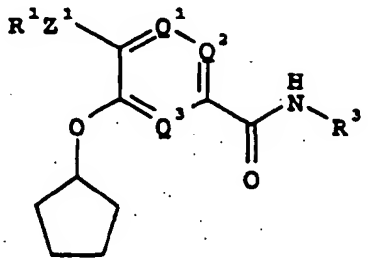
For example, intermediates of formula (II, T^2-CF=NR^3) wherein T^2 and R^3 are as hereinbefore defined and R^3 preferably represents a heteroaryl group containing at least one nitrogen atom, preferably a substituted heteroaryl group containing at least one nitrogen atom wherein the substitution is such that the pKa of the said nitrogen atom is about 10 or less, e.g. a

3,5-dichloropyrid-4-yl group, may conveniently be prepared by reaction of compounds of the general formula (1):-

$$T^2\text{-}CONHR^3 \qquad (1)$$

wherein T^2 and R^3 are as immediately hereinbefore defined with diethylaminosulphur trifluoride. The reaction preferably takes place in an inert solvent, such as dichloromethane, preferably at a temperature from about 0°C to about room temperature.

Compounds of formula (1) wherein T^2 and R^3 are as hereinbefore defined, may be prepared from compounds of the general formula (2):-



(2)

wherein R^1, R^3, Q^1, Q^2, Q^3, and Z^1 are as hereinbefore defined, by treatment with aluminium chloride. The reaction preferably takes place in an inert solvent, such as dichloromethane, preferably at a temperature from about 0°C to about room temperature.

Compounds of formula (2) wherein R^1, R^3, Q^1, Q^2, Q^3, and Z^1 are as hereinbefore defined may be prepared as described in the specification of International Patent Application Publication No. WO 92/12961.

Intermediates of formula (III) wherein R^2 is an alkyl-, aryl-, or heteroaryl-1,2,4-oxadiazole or an aryl-, or heteroaryl-1,3,4-oxadiazole, and A^1 is an alkylene linkage may be prepared by hydrolysis of compounds of formula (3):-

$$R^2\text{-}A^1OCOCH_3 \qquad (3)$$

wherein R^2 is aryl or heteroaryl and A^1 is an alkylene linkage. The hydrolysis may conveniently be carried out by alkaline hydrolysis using a base, such as an alkali metal hydroxide or carbonate, in the presence of an aqueous/organic solvent mixture, using organic solvents such as acetonitrile, dioxan, tetrahydrofuran or methanol, at a temperature from about ambient to about reflux.

Compounds of formula (3) wherein R^2 is an alkyl-, aryl-, or heteroaryl-1,2,4-oxadiazole and A^1 is an alkylene linkage, may be prepared by reaction of an alkyl-, aryl- or heteroarylamidoxime (which may be prepared by reaction of the corresponding alkyl-, aryl- or heteroarylnitrile with hydroxylamine hydrochloride in the presence of an alkali metal hydroxide, such as sodium hydroxide, in aqueous ethanol at a temperature at about reflux) with an acetoxyalkanoyl chloride according to the procedure of G.D.Diana et al J.Med.Chem., 1994, 37, 2421-2436.

Compounds of formula (3), wherein R^2 represents a 2-aryl- or 2-heteroaryl-1,3,4-oxadiazol-5-yl group and A^1 is an alkylene linkage, may be prepared by dehydration of compounds of formula (4):-

$$R^8CONHNHCOA^1OCOCH_3 \qquad (4)$$

wherein R^8 represents aryl or heteroaryl and A^1 is an alkylene linkage. The reaction is carried in the presence of 4-toluene sulphonic acid in an inert solvent, such as toluene, at a temperature at about 125°C.

Compounds of formula (4) wherein R^8 represents aryl or heteroaryl and A^1 is an alkylene linkage may be prepared by reaction of aryl- or heteroaryl-acid hydrazides with an acetoxyalkanoyl chloride in the presence of an organic base, such as pyridine, in an inert solvent, such as dichloromethane, at a temperature at about 0°C to about room temperature.

Intermediates of formula (IV, T^1-COX^4) wherein T^1 is as hereinbefore defined and X^4 represents a halogen atom may be prepared from compounds of the general formula (5):-

$$T^1\text{-}COOH \qquad (5)$$

wherein T^1 is as hereinbefore defined, by the application or adaptation of known methods for the preparation of acid halides from carboxylic acids. For example, when X^4 represents a chlorine atom, the reaction may be carried out by means of thionyl chloride or, preferably, oxalyl chloride, optionally in the presence of a small amount of dimethylformamide.

Intermediates of formula (IV, T^1-COX^4) wherein T^1 is as hereinbefore defined and X^4 represents an azido group may be prepared from compounds of formula (5) wherein T^1 is as hereinbefore defined by the application or adaptation of known methods for the preparation of acid azides from carboxylic acids. For example, the reaction may be carried out by means of diphenylphosphoryl azide in the presence of triethylamine in dimethylformamide.

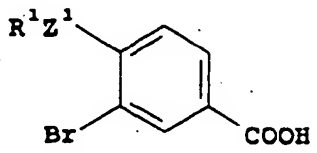
Compounds of formula (5) wherein T^1 is as hereinbefore defined, and preferably Z^1 and Z^2 represent oxygen atoms, may be prepared by the oxidation of intermediates of formula (XIX, T^1-CHO) wherein T^1 is as hereinbefore defined, and preferably Z^1 and Z^2 represent oxygen atoms, e.g. by reaction with potassium permanganate, or with a mixture of sulphamic acid and sodium chlorite in acetic acid, or with sodium chlorite in the presence of sodium dihydrogen phosphate, preferably in the presence of an alkene, e.g. 2-methylbut-2-ene, conveniently in t-butanol.

Alternatively, compounds of formula (5) wherein T^1 is as hereinbefore defined may be prepared by the hydrolysis of intermediates of formula (VI, T^1-COOR^5) wherein T^1 and R^5 are as hereinbefore defined, for example by reaction with a base, such as an alkali metal hydroxide, carbonate or bicarbonate in the presence of water, in an alcohol such as methanol and at a temperature from about ambient to about reflux, followed by reaction with an aqueous acid such as dilute hydrochloric acid.

Alternatively, compounds of formula (5) wherein T^1 is as hereinbefore defined, but where Z^2 represents a direct bond and A^1 represents a straight- or branched- carbon chain comprising from 2 to about 6 carbon atoms, may be prepared by hydrogenation of compounds of formula (5), wherein T^1 is as hereinbefore defined, but where Z^2 represents a direct bond and A^1 represents a straight- or branched- carbon chain comprising from 2 to about 6 carbon atoms which contains a double or triple carbon-carbon bond. The hydrogenation may be carried out using hydrogen in the presence of a suitable metal catalyst, e.g. platinum or palladium optionally supported on an

inert carrier such as carbon, preferably in a solvent such as methanol or ethanol.

Alternatively, compounds of formula (5) wherein T^1 is as hereinbefore defined, but where Z^2 and A^1 each represent a direct bond and Q^1, Q^2 and Q^3 each represent CH, may be prepared from compounds of formula (6):-



(6)

wherein R^1, R^5 and Z^1 are as hereinbefore defined, by reaction with compounds of formula (7):-

$$R^2\text{-}B(OH)_2 \qquad (7)$$

wherein R^2 is as hereinbefore defined, in the presence of a complex metal catalyst such as tetrakis(triphenylphosphine)palladium(0).

According to a feature of the invention, intermediates of formula (V, R^3NHR^4) wherein R^3 represents a 3,5-dihalo-1-oxido-4-pyridinio group and R^4 represents a lower alkanoyl, preferably acetyl, group may be prepared by treatment of the corresponding compounds of formula (V) wherein R^3 is as hereinbefore defined and R^4 is hydrogen with an alkanoyl halide, for example acetyl chloride when R^4 represents an acetyl group. The reaction may be preferably carried out in the presence of a base such as an alkali metal hydride, e.g. sodium hydride optionally in an inert solvent, for example

dimethylformamide, or an ether, for example tetrahydrofuran, preferably at a temperature from 0°C to about 50°C.

According to a further feature of the invention, intermediates of formula (V, R^3NHR^4) wherein R^3 represents a 3,5-dichloro-1-oxido-4-pyridinio group and R^4 represents a lower alkanoyl group, preferably acetyl, may be prepared by oxidation of the corresponding compounds of formula (V) wherein R^3 represents a 3,5-dihalo-4-pyridyl group and R^4 represents a lower alkanoyl group. The oxidation may be carried out by means of reaction with a mixture of hydrogen peroxide and an organic acid, e.g. acetic acid, preferably at or above room temperature at 60-90°C. Alternatively, the oxidation may be carried out by reacting a peracid, for example m-chloroperoxybenzoic acid, in an inert solvent such as dichloromethane, at a temperature from about room temperature to reflux, preferably at elevated temperature. The oxidation may also be carried out by reaction with hydrogen peroxide in the presence of sodium tungstate at temperatures between room temperature and about 60°C.

Intermediates of formula (XIX, T^1-CHO) wherein T^1 is as hereinbefore defined, but where Z^2 represents oxygen and A^1 represents a straight- or branched-chain alkylene linkage, may be prepared from compounds of the general formula (8):-

$$T^2\text{-CHO} \qquad (8)$$

wherein T^2 is as hereinbefore defined, by reaction with a compound of formula (XXII, $R^2A^1X^{10}$) wherein R^2 and X^{10} are as hereinbefore defined, X^{10} preferably representing a bromine atom, and A^1 represents a straight- or branched-chain alkylene linkage. The alkylation may be carried out preferably in the presence of a base, for example an alkali metal hydride, e.g.

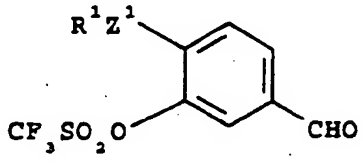
sodium hydride, an alkali metal hydroxide or sodium carbonate, e.g. sodium hydroxide or carbonate, or an amine, preferably a tertiary amine, e.g. triethylamine or pyridine, optionally in an inert solvent, for example dichloromethane, dimethylformamide, or an ether, e.g. diethyl ether or tetrahydrofuran, preferably at a temperature from 0°C to the reflux temperature.

Alternatively, intermediates of formula (XIX, T^1-CHO) wherein T^1 is as hereinbefore defined, but where Z^2 represents an oxygen atom and A^1 represents a straight- or branched-chain alkylene linkage, may be prepared from compounds of formula (8, T^2-CHO) wherein T^2 is as hereinbefore defined by reaction with compounds of formula (III, R^2A^1OH) wherein R^2 is as hereinbefore defined and A^1 represents a straight- or branched-chain alkylene linkage. The reaction may be carried out in the presence of a triarylphosphine, such as triphenylphosphine, and a dialkyl ester, such as the diisopropyl or diethyl ester of azodicarboxylic acid. The reaction preferably takes place in an inert solvent, such as tetrahydrofuran, preferably at a temperature from about 0°C to about 60°C.

Intermediates of formula (XIX, T^1-CHO) wherein T^1 is as hereinbefore defined, but where Z^2 represents an oxygen atom and A^1 represents a direct bond, and R^2 represents a partially saturated bicycloaryl group (e.g. 2-indanyl), may be prepared from compounds of formula (8, T^2-CHO) wherein T^2 is as hereinbefore defined by reaction with a partially saturated bicycloarylalcohol (e.g.2-indanol). The reaction may be carried out in the presence of a triarylphosphine, such as triphenylphosphine, and a dialkyl ester, such as the diisopropyl or diethyl ester of azodicarboxylic acid. The reaction preferably takes place in an inert solvent, such as

tetrahydrofuran, preferably at a temperature from about 0°C to about 60°C.

Intermediates of formula (XIX, T^1-CHO) wherein T^1 is as hereinbefore defined, but where A^1 represents an ethynylene linkage and Z^2 represents a direct bond, may be prepared from compounds of formula (9):-



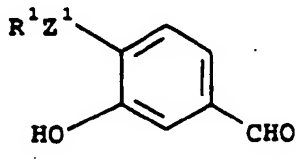
(9)

wherein R^1 and Z^1 are as hereinbefore defined, by reaction with compounds of formula (10):-

$$R^2\text{-}C{\equiv}C\text{-}H \qquad (10)$$

wherein R^2 is as hereinbefore defined. The reaction is carried out in the presence of bis(triphenylphosphine)palladium(II) chloride and triethylamine. The reaction preferably takes place in an inert solvent, such as dimethylformamide, preferably at a temperature at about 90°C.

Compounds of formula (9), wherein R^1 and Z^1 are as hereinbefore defined, may be prepared by reaction of compounds of formula (11):-



(11)

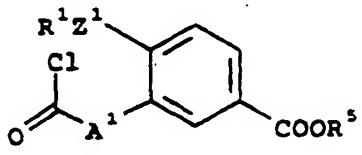
wherein R^1 and Z^1 are as hereinbefore defined, with trifluoromethanesulphonic anhydride in the presence of an organic base, such as pyridine, at a temperature from about -10°C to about room temperature.

Intermediates of formula (VI, T^1-$COOR^5$) wherein T^1 and R^5 are as hereinbefore defined, but where Z^2 represents an oxygen atom, may be prepared from compounds of the general formula (12):-

$$T^2\text{-}COOR^5 \qquad (12)$$

wherein T^2 and R^5 are as hereinbefore defined, by reaction with compounds of formula (III) wherein R^2 and A^1 are as hereinbefore defined, in the presence of a triarylphosphine, such as triphenylphosphine, and a dialkyl ester, such as the diisopropyl or diethyl ester of azodicarboxylic acid. The reaction preferably takes place in an inert solvent, such as tetrahydrofuran, preferably at a temperature from about 0°C to about 60°C.

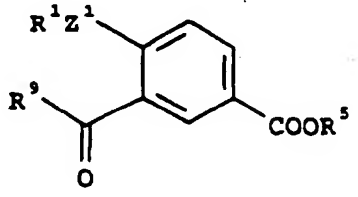
Intermediates of formula (VI, T^1-$COOR^5$) wherein T^1 and R^5 are as hereinbefore defined, but where Q^1, Q^2 and Q^3 each represent CH and Z^2 represents a direct bond, may be prepared from compounds of formula (13):-



(13)

wherein R^1, R^5, A^1 and Z^1 are as hereinbefore defined, by reaction with an alkyl-, aryl- or heteroarylamidoxime (which may be prepared by reaction of the corresponding alkyl-, aryl- or heteroarylnitrile with hydroxylamine hydrochloride in the presence of an alkali metal hydroxide such as sodium hydroxide, in aqueous ethanol at a temperature at about reflux). The reaction preferably takes place in an inert solvent, such as tetrahydrofuran, in the presence of pyridine, at a temperature from about ambient to about reflux.

Compounds of formula (VI, T^1-$COOR^5$) wherein T^1 and R^5 are as hereinbefore defined but where Q^1, Q^2 and Q^3 each represent CH, Z^2 represents a direct bond, and A^1 represents a $-C(R^9)=C(R^{10})-(CH_2)_n-$ linkage (where R^9 and R^{10} independently represent H or alkyl and n is 0, 1, 2, or 3), may be prepared from compounds of formula (14):-



(14)

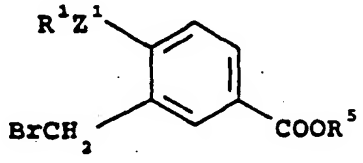
wherein R^1, R^5, R^9, Z^1, are as hereinbefore defined, by reaction with the reaction product of a compound of formula (15):-

$$[(R^{11})_3PCH(R^{10})(CH_2)_nR_2]^+ \quad (X^{11})^- \qquad (15)$$

wherein R^2, R^9 and n are as hereinbefore defined, R^{11} represents an aryl, such as phenyl group, and X^{11} represents halo, preferably bromo, with a base such as an alkali metal alkoxide (for example potassium t-butoxide), or an alkali

metal hydride (for example sodium hydride), or butyl lithium. The reaction is preferably carried out in a solvent such as dimethylformamide or tetrahydrofuran.

Intermediates of formula (VI, T^1-$COOR^5$) wherein T^1 and R^5 are as hereinbefore defined but where Q^1, Q^2 and Q^3 each represent CH, Z^2 represents a direct bond, and A^1 represents a $-(CH_2)_n-SCH_2-$ linkage, may be prepared by the reaction of compounds of the general formula (16):-



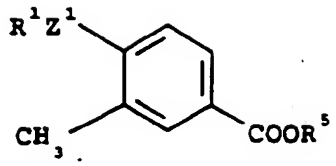
(16)

wherein R^1 and Z^1 are as hereinbefore defined, with compounds of general formula (17):-

$$R^2-(CH_2)_n-SH \qquad (17)$$

wherein R^2 is as hereinbefore defined, in the presence of a base such as sodium hydride. The reaction takes place in an inert solvent, such as an ether, for example tetrahydrofuran, at a temperature from about 0°C to about reflux.

Compounds of the general formula (16) wherein R^1 and Z^1 are as hereinbefore defined, may be prepared by the reaction of compounds of the general formula (18):-



(18)

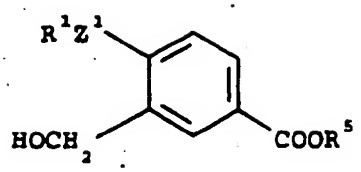
wherein R^1 and Z^1 are as hereinbefore defined, with N-bromosuccinimide in the presence of benzoyl peroxide. The reaction takes in a chlorinated hydrocarbon solvent, for example chloroform, at a temperature at about reflux.

Intermediates of formula (VI, T^1-$COOR^5$) wherein T^1 and R^5 are as hereinbefore defined but where Q^1, Q^2 and Q^3 each represent CH, Z^2 represents a direct bond, and A^1 represents a $-(CH_2)_n-OCH_2-$ linkage, may be prepared by the reaction of compounds of the general formula (16), wherein R^1, R^5 and Z^1 are as hereinbefore defined, with compounds of general formula (19):-

$$R^2-(CH_2)_n-OH \qquad (19)$$

wherein R^2 is as hereinbefore defined, in the presence of a base such as sodium hydride. The reaction takes place in an inert solvent, such as an ether, for example tetrahydrofuran, at a temperature from about 0°C to about reflux.

Intermediates of formula (VI, T^1-$COOR^5$) wherein T^1 is as hereinbefore defined but where Q^1, Q^2 and Q^3 each represent CH, Z^2 represents a direct bond, and A^1 represents a $-(CH_2)_n-OCH_2-$ linkage, may be prepared by the reaction of compounds of the general formula (20):-



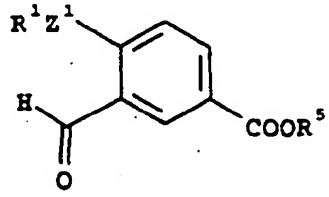
(20)

wherein R^1 and Z^1 are as hereinbefore defined, with compounds of general formula (21):-

$$R^2-(CH_2)_n-X^{12} \qquad (21)$$

wherein R^2 is as hereinbefore defined and X^{12} represents a halogen atom, preferably a bromine atom, in the presence of a base such as sodium hydride. The reaction takes place in an inert solvent, such as an ether, for example tetrahydrofuran, at a temperature from about 0°C to about reflux.

Compounds of formula (20), wherein R^1 and Z^1 are as hereinbefore defined, may be prepared by reduction of compounds of formula (22):-



(22)

wherein R^1 and Z^1 are as hereinbefore defined, with sodium borohydride in methanol.

Intermediates of formula (VIII, T^1-CH(OH)CH_2R^3) wherein T^1 and R^3 are as hereinbefore defined may be prepared by the reaction of compounds of the general formula (23):-

T^1-X^{13} (23)

wherein T^1 is as hereinbefore defined and X^{13} represents halo, e.g. bromine, with compounds of the general formula (24):-

R^3CH_2CHO (24)

wherein R^3 is as hereinbefore defined, in the presence of a base such as butyl lithium. The reaction takes place in an inert solvent, such as an ether, for example tetrahydrofuran, preferably at a temperature lower than -65°C.

Alternatively, intermediates of formula (VIII, $T^1-CH(OH)CH_2R^3$) wherein T^1 and R^3 are as hereinbefore defined may be prepared by the reaction of compounds of formula (XIX, T^1-CHO) wherein T^1 is as hereinbefore defined, with compounds of formula (VII, R^3-CH_3) wherein R^3 is as hereinbefore defined, in the presence of a base such as lithium diisopropylamide (usually prepared in situ from butyl lithium and diisopropylamine). The reaction takes place in an inert solvent, such as an ether, for example tetrahydrofuran, preferably at a temperature lower than -65°C.

Intermediates of formula (IX, $T^1-CZNR^6OR^7$), wherein T1, R^6 and R^7 are as hereinbefore described and Z represents an oxygen atom, may be prepared by the reaction of compounds of the general formula (V, T^1-COX^4), wherein T^1 is as hereinbefore defined and X^4 is a halogen atom, such as a chlorine atom, with an N-alkyl-O-alkylhydroxylamine, e.g. N-methyl-O-methylhydroxylamine, in an inert solvent such as dimethylformamide.

Intermediates of formula (X, T^1-CN), wherein T^1 is as hereinbefore described, may be prepared by the reaction of compounds of the general formula (XIX) with nitroethane and sodium acetate in acetic acid according to the method of S.N.Karmarker, Synthesis, 1985, p.510.

Intermediates of formula (XII, T^1-$CONH_2$), wherein T^1 is as hereinbefore described, may be prepared by the reaction of compounds of the general formula (X, T^1-CN) with hydrogen peroxide and an alkali metal hydroxide, such as potassium hydroxide, in water according to the method of J.S.Buck, Organic Synthesis, 1943, p.44.

Intermediates of formula (XIV, T^1-OH), wherein T^1 is as hereinbefore described, may be prepared by the reaction of compounds of the general formula (XIX, T^1-CHO) with hydrogen peroxide and an alkali metal hydroxide, such as potassium hydroxide, in water according to the procedure described in the specification of Patent Application No.EP25659.

Intermediates of formula (XVII, T^1-NH_2), wherein T^1 is as hereinbefore defined, may be prepared by hydrogenation of compounds of formula (25):-

$$T^1\text{-}NO_2 \qquad (25)$$

wherein T^1 is as hereinbefore defined. The hydrogenation may be carried out using hydrogen in the presence of a suitable metal catalyst, e.g. palladium optionally supported on an inert carrier such as carbon, preferably in a solvent such as methanol or ethanol.

Compounds of formula (25), wherein T^1 is as hereinbefore defined, but where R^1 is methyl, Z^1 and Z^2 represents an oxygen atom, Q^1, Q^2 and Q^3 each represent a CH linkage and A^1 represents a straight- or branched-chain alkylene linkage, may be prepared from 3-hydroxy-4-methoxynitrobenzene by reaction with a compound of formula (XXII, $R^2A^1X^{10}$) wherein R^2, X^{10} are as hereinbefore defined and A^1 represents a straight- or branched-chain alkylene linkage. The alkylation may be carried out preferably in the presence of a base, for example an alkali metal hydride, e.g. sodium hydride, an alkali metal hydroxide or sodium carbonate, e.g. sodium hydroxide or carbonate, or an amine, preferably a tertiary amine, e.g. triethylamine or pyridine, optionally in an inert solvent, for example dichloromethane, dimethylformamide, or an ether, e.g. diethyl ether or tetrahydrofuran, preferably at a temperature from 0°C to the reflux temperature.

Alternatively, compounds of formula (25) wherein T^1 is as hereinbefore defined, but where R^1 is methyl, Z^1 and Z^2 represents an oxygen atom, Q^1, Q^2 and Q^3 each represent a CH linkage and A^1 represents a straight- or branched-chain alkylene linkage, may be prepared from 3-hydroxy-4-methoxynitrobenzene by reaction with compounds of formula (III, R^2A^1OH) wherein R^2 is as hereinbefore defined and A^1 represents a straight- or branched-chain alkylene linkage. The reaction may be carried out in the presence of a triarylphosphine, such as triphenylphosphine, and a dialkyl ester, such as the diisopropyl or diethyl ester of azodicarboxylic acid. The reaction preferably takes place in an inert solvent, such as tetrahydrofuran, preferably at a temperature from about 0°C to about 60°C.

Intermediates of formula (XX, T^1-CH_2X^9), wherein T^1 is as hereinbefore described and X^9 is a bromine atom, may be prepared by bromination of compounds of formula (26):-

T^1-CH_3 (26)

wherein T^1 is as hereinbefore described, with N-bromosuccinimide, optionally in the presence of a catalyst, such as benzoyl peroxide, in an inert solvent such as dichloromethane and at a temperature at about room temperature to about reflux temperature.

Compounds of formula (26,T^1-CH_3), wherein T^1 is as hereinbefore defined, but where R^1 is methyl, Z^1 and Z^2 represents an oxygen atom, Q^1, Q^2 and Q^3 each represent a CH linkage and A^1 represents a straight- or branched-chain alkylene linkage, may be prepared by reaction of 2-methoxy-5-methylphenol with compounds of formula (III, R^2A^1OH) wherein R^2 is as hereinbefore defined A^1 represents a straight- or branched-chain alkylene linkage. The reaction may be carried out in the presence of a triarylphosphine, such as triphenylphosphine, and a dialkyl ester, such as the diisopropyl or diethyl ester of azodicarboxylic acid. The reaction preferably takes place in an inert solvent, such as tetrahydrofuran, preferably at a temperature from about 0°C to about 60°C.

Alternatively, compounds of formula (26, T^1-CH_3), wherein T^1 is as hereinbefore defined, but where R^1 is methyl, Z^1 and Z^2 represents an oxygen atom, Q^1, Q^2 and Q^3 each represent a CH linkage and A^1 represents a straight- or branched-chain alkylene linkage, may be prepared by reaction of 2-methoxy-5-

methylphenol with compounds of formula (XXII, $R^2A^1X^{10}$) wherein R^2, X^{10} are as hereinbefore defined and A^1 represents a straight- or branched-chain alkylene linkage. The alkylation may be carried out preferably in the presence of a base, for example an alkali metal hydride, e.g. sodium hydride, an alkali metal hydroxide or sodium carbonate, e.g. sodium hydroxide or carbonate, optionally in an inert solvent, for example dimethylformamide, or an ether, e.g. diethyl ether or tetrahydrofuran, preferably at a temperature from 0°C to the reflux temperature.

Intermediates of formula (XXIII, T^1-SH), wherein T^1 is as hereinbefore described, may be prepared from compounds of formula (XXX, T^1-I), wherein T^1 is as hereinbefore, by reaction with sodium thiobenzoate and subsequent hydrolysis (as described by A.Osuka et.al. Synthesis, 1983,p.68).

Intermediates of formula (XXIV, T^1-CF_2Br) wherein T^1 is as hereinbefore defined may be prepared from compounds of the general formula (27):-

$$T^1\text{-}CHF_2 \qquad (27)$$

wherein T^1 is as hereinbefore defined, by reaction with bromine in carbon tetrachloride and ultraviolet radiation, at a temperature from about ambient to about reflux.

Compounds of formula (27) wherein T^1 is as hereinbefore defined may be prepared by the action of sulphur tetrafluoride and hydrofluoric acid on compounds of formula (XIX, T^1-CHO) wherein T^1 is as hereinbefore defined, in the presence of pyridine, at or below room temperature, or alternatively by the action of diethylaminosulphur trifluoride, preferably in an inert

solvent, such as dichloromethane, preferably at a temperature from about 0°C to about room temperature.

Intermediates of the general formula (XXVI, T^1-NCO) wherein T^1 is as hereinbefore defined may be prepared by treatment of compounds of formula (XVII, T^1-NH_2) wherein T^1 is as hereinbefore defined with the phosgene equivalent ($ClC(=O)OCCl_3$) in an inert solvent such as dioxan at a temperature at about 60°C.

Intermediates of formula (XXX, T^1-I), wherein T^1 is as hereinbefore described and A^1 represents a straight- or branched-chain alkylene linkage, may be prepared by alkylation of 5-iodo-2-methoxyphenol with compounds of formula (XXII, $R^2A^1X^{10}$) wherein R^2, X^{10} are as hereinbefore defined and A^1 represents a straight- or branched-chain alkylene linkage. The alkylation may be carried out preferably in the presence of a base, for example an alkali metal hydride, e.g. sodium hydride, an alkali metal hydroxide or sodium carbonate, e.g. sodium hydroxide or carbonate, optionally in an inert solvent, for example dimethylformamide, or an ether, e.g. diethyl ether or tetrahydrofuran, preferably at a temperature from 0°C to the reflux temperature.

Intermediates of formula (XXXII, T^1-CH_2OH), wherein T^1 is as hereinbefore described may be prepared by reduction of compounds of formula (VI, T^1-$COOR^5$) with lithium aluminium hydride in an inert solvent, such as diethyl ether, at a temperature from about room temperature to about reflux.

Alternatively compounds of formula (XXXII, T^1-CH_2OH), wherein T^1 is as hereinbefore described, may be prepared by the

reduction of compounds of formula (XIX, T^1-CHO), preferably by means of reaction with an alkali metal borohydride, preferably in an inert solvent, e.g. tetrahydrofuran, and preferably at or near room temperature.

Intermediates of formula (XXXIII, T^1-COCOOH), wherein T^1 is as hereinbefore defined, but where R^1 is a methyl group, Z^1 and Z^2 represent oxygen atoms, and A^1 represents a straight- or branched-chain alkylene linkage, may be prepared by the oxidation of compounds of the general formula (28):-

$$T^1\text{-}COCH_3 \qquad (28)$$

wherein T^1 is as hereinbefore defined, but where R^1 is a methyl group, Z^1 and Z^2 represent oxygen atoms, and A^1 represents a straight- or branched-chain alkylene linkage,, by reaction with selenium dioxide in the presence of pyridine, in mild conditions, e.g. in a solvent such as ethanol, at or below room temperature.

Compounds of the general formula (28), wherein T^1 is as hereinbefore defined, but where R^1 is a methyl group, Z^1 and Z^2 represent oxygen atoms, and A^1 represents a straight- or branched-chain alkylene linkage, may be prepared by alkylation of 3-hydroxy-4-methoxyacetophenone with compounds of formula (XXII, $R^2A^1X^{10}$) wherein R^2, X^{10} are as hereinbefore defined and A^1 represents a straight- or branched-chain alkylene linkage. The alkylation may be carried out preferably in the presence of a base, for example an alkali metal hydride, e.g. sodium hydride, an alkali metal hydroxide or sodium carbonate, e.g. sodium hydroxide or carbonate, optionally in an inert solvent, for example dimethylformamide, or an ether, e.g. diethyl ether

or tetrahydrofuran, preferably at a temperature from 0°C to the reflux temperature.

Intermediates of formula (XXXIV, T^1-N_2^+ BF_4^-), wherein T^1 is as hereinbefore defined may be prepared by diazotisation of compounds of formula (XVII, T^1-NH_2) with sodium nitrite in the presence of hydrochloric acid, followed by treatment with sodium tetrafluoroborate.

Intermediates of formula (XXXVII, T^1-CH_2-CH(OH)-R^3) wherein T^1 and R^3 are as hereinbefore defined may be prepared by reaction of compounds of formula (29):-

$$T^1\text{-}CH_2CHO \qquad (29)$$

wherein T^1 is as hereinbefore defined, with compounds of formula (XXV, R^3OH) wherein R^3 is as hereinbefore defined in the presence of a base such as lithium diisopropylamide.

Compounds of general formula (V) wherein R^3 represents a 3,5-dihalo-1-oxido-4-pyridinio group, more especially a 3,5-dichloro-1-oxido-4-pyridinio group, and R^4 represents a lower alkanoyl group, more especially an acetyl group are key intermediates and, as such, they and their preparation as described herein constitute further features of the present invention.

Intermediates of formulae (II), (IV), (VI), (VIII), (IX), (X), (XII), (XIV), (XVII), (XIX), (XX), (XXIII), (XXIV), (XXVI), (XXX), (XXXII), (XXXIII), (XXXIV), (XXXVII), (5), (23), (25), (26), (27), (28), and (29) are novel compounds and, as such,

they and processes described herein for their preparation constitute further features of the present invention.

The present invention is further illustrated but not limited by the following Examples and Reference Examples.

EXAMPLE 1

(a) 3-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-ylmethoxy]-N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxybenzamide

A solution of 3-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-ylmethoxy]-N-(3,5-dichloropyridin-4-yl)-4-methoxybenzamide [0.29g, Example 6(a)] in dichloromethane (30ml), heated at reflux, was treated portionwise with 3-chloroperoxybenzoic acid (0.2g, 50%). The mixture was heated at reflux for 2 hours, then treated with another aliquot of 3-chloroperoxybenzoic acid, and then refluxed for a further 1.5 hours. The mixture was treated with a further aliquot of 3-chloroperoxybenzoic acid and then left standing at ambient temperature overnight. An additional aliquot of 3-chloroperoxybenzoic acid was added and then the mixture was refluxed for 8 hours. After standing at ambient temperature for 3 days saturated aqueous sodium bicarbonate (50ml) was added. The reaction mixture was stirred for 15 minutes then treated with sodium sulphite until the solution was negative to starch iodide paper. The organic phase was separated, then washed with water (20ml), then dried over magnesium sulphate and then evaporated. The residual pale yellow solid was recrystallised from a mixture of ethanol and water affording the title compound (0.12g) as colourless crystals, m.p. 210-211°C. [Elemental analysis:- C,50.4; H,2.90; N,10.70%. Calculated:- C,50.6; H,2.90; N,10.74%].

(b) By proceeding in a similar manner to Example 1(a) but using 3-{2-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]ethyl}-N-(3,5-dichloropyridin-4-yl)-4-methoxybenzamide [Example 7(a)] there was prepared 3-{2-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-

yl]ethyl]-N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxybenzamide, which was recrystallised from isopropanol as colourless crystals, m.p. 197-198°C. [Elemental analysis:- C,53.15; H,3.30; N,10.78%. Calculated:- C,53.15; H,3.39; N,10.42%];

(c) By proceeding in a similar manner to Example 1(a) but using N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[2-(pyridin-3-yl)ethoxy]benzamide [Example 7(f)], and carrying out the reaction at ambient temperature, then subjecting the product of the reaction to reverse phase high pressure liquid chromatography (Dynamax-60Å C_{18} column) eluting with a mixture of methanol and water (3:2, v/v), there was prepared N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[2-(1-oxido-3-pyridinio)ethoxy]benzamide as a white solid, m.p. 147-150°C. [Elemental analysis:- C,52.6; H,3.9; N,9.25%. Calculated for $C_{20}H_{17}Cl_2N_3O_4 \cdot 1.14H_2O$:- C,52.8; H,4.3; N,9.2%];

(d) By proceeding in a similar manner to Example 1(a) but using N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[2-(pyridin-3-yl)ethoxy]benzamide [Example 7(f)] there was prepared N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-[2-(1-oxido-3-pyridinio)ethoxy]benzamide as an off-white solid, m.p. 196-198°C. [Elemental analysis:- C,52.2; H,3.7; N,8.9%. Calculated for $C_{20}H_{17}Cl_2N_3O_5 \cdot 0.46H_2O$:- C,52.4; H,3.9; N,9.2%];

(e) By proceeding in a similar manner to Example 1(a) but using 2-(3,5-dichloropyridin-4-yl)-1-[4-methoxy-3-[2-(pyridin-3-yl)ethoxy]phenyl]ethanone [Example 10] and carrying out the reaction at ambient temperature, there was prepared 2-(3,5-dichloropyridin-4-yl)-1-[4-methoxy-3-[2-(1-oxido-3-pyridinio)ethoxy]phenyl]ethanone as a white solid, m.p. 127-

129°C. [Elemental analysis:- C,58.1; H,4.2; N,6.3%. Calculated:- C,58.2; H,4.2; N,6.5%];

(f) By proceeding in a similar manner to Example 1(a) but using 2-(3,5-dichloropyridin-4-yl)-1-{4-methoxy-3-[2-(pyridin-2-yl)ethoxy]phenyl}ethanone [Example 9], and carrying out the reaction at ambient temperature then subjecting the product to reverse phase high pressure liquid chromatography (Dynamax-60Å C_{18} column) eluting with a mixture of methanol and water (7:3, v/v), there was prepared 2-(3,5-dichloropyridin-4-yl)-1-{4-methoxy-3-[2-(1-oxido-2-pyridinio)ethoxy]phenyl}ethanone as a white solid, m.p. 135-136°C. [Elemental analysis:- C,58.3; H,4.25; N,6.4%. Calculated:- C,58.2; H,4.2; N,6.5%];

(g) By proceeding in a similar manner to Example 1(a) but using 2-(3,5-dichloropyridin-4-yl)-1-{4-methoxy-3-[2-(pyridin-2-yl)ethoxy]phenyl}ethanone (Example 9) there was prepared 2-(3,5-dichloro-1-oxido-4-pyridinio)-1-{4-methoxy-3-[2-(1-oxido-2-pyridinio)ethoxy]phenyl}ethanone as a white solid, m.p. 169-171°C. [Elemental analysis: C,56.2;H,4.1;N,6.0%; Calculated: C,56.1;H,4.0;N,6.2%].

(h) By proceeding in a similar manner to Example 1(a) but using N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[4-phenylbutoxy]benzamide [Example 6(g)] there was prepared N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(4-phenylbutoxy)benzamide, which was recrystallised from ethyl acetate as off-white crystals, m.p. 151-152°C. [Elemental analysis:- C,59.88; H,4.81; N,6.07%. Calculated for $C_{23}H_{22}Cl_2N_2O_4$:- C,60.08; H,4.64; N,6.12%];

(i) By proceeding in a similar manner to Example 1(a) but using N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(phenoxymethyl)benzamide [Example 7(i)] there was prepared

N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(phenoxymethyl)benzamide, which was recrystallised from acetonitrile as colourless crystals, m.p. 160-161°C. [Elemental analysis:- C,57.40; H,3.82; N,6.68%. Calculated for $C_{20}H_{16}Cl_2N_2O_4$:- C,57.30; H,3.85; N,6.68%];

(j) By proceeding in a similar manner to Example 1(a) but using N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-benzyloxyethoxy)benzamide [Example 6(i)] there was prepared N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(2-benzyloxyethoxy)benzamide, which was recrystallised from acetonitrile as colourless crystals, m.p. 168-169°C. [Elemental analysis:- C,57.03; H,4.35; N,6.04%. Calculated for $C_{22}H_{20}Cl_2N_2O_5$:- C,57.61; H,4.53; N,6.25%];

(k) By proceeding in a similar manner to Example 1(a) but using N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-benzyloxymethyl)benzamide [Example 7(j)] there was prepared N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(2-benzyloxymethyl)benzamide, which was recrystallised from ethyl acetate as colourless crystals, m.p. 160-161°C. [Elemental analysis:- C,58.21; H,4.19; N,6.47%. Calculated for $C_{21}H_{18}Cl_2N_2O_4$:- C,58.47; H,4.20; N,6.71%];

(l) By proceeding in a similar manner to Example 1(a) but using N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(4-methoxyphenyl)benzamide [Example 7(k)] there was prepared N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(4-methoxyphenyl)benzamide, which was recrystallised from acetonitrile as a pale cream solid, m.p. 206-208°C. [Elemental analysis:- C,57.36; H,3.91; N,7.02%. Calculated for $C_{20}H_{16}Cl_2N_2O_4$:- C,57.30; H,3.85; N,6.68%];

(m) By proceeding in a similar manner to Example 1(a) but using N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-ylmethoxy)benzamide [Example 7(n)] there was prepared N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-ylmethoxy)benzamide, as a pale yellow solid, m.p. 195-197°C. [Elemental analysis:- C,53.75; H,3.67; N,10.83%. Calculated for $C_{23}H_{18}Cl_2N_4O_6$:- C,53.40; H,3.51; N,10.95%];

(n) By proceeding in a similar manner to Example 1(a) but using N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(pyridin-2-ylmethoxy)benzamide [Example 8(p)], and carrying out the reaction at ambient temperature, there was prepared N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(pyridin-2-ylmethoxy)benzamide, as a white solid, m.p. 203°C. [Elemental analysis:- C,54.05; H,3.68; N,9.86%. Calculated for $C_{19}H_{15}Cl_2N_3O_4$:- C,54.30; H,3.60; N,10.00%];

(o) By proceeding in a similar manner to Example 1(a) but using N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(pyridin-3-ylmethoxy)benzamide [Example 8(q)], and carrying out the reaction at ambient temperature, there was prepared N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(pyridin-3-ylmethoxy)benzamide, as a white solid, m.p. 181°C. [Elemental analysis:- C,53.90; H,3.69; N,10.06%. Calculated for $C_{19}H_{15}Cl_2N_3O_4$:- C,54.30; H,3.60; N,10.00%];

(p) By proceeding in a similar manner to Example 1(a) but using N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(pyridin-4-ylmethoxy)benzamide [Example 8(r)], and carrying out the reaction at ambient temperature, there was prepared N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(pyridin-4-ylmethoxy)benzamide, as a white solid, m.p. 213°C.

(q) By proceeding in a similar manner to Example 1(a) but using N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(pyridin-2-ylmethoxy)benzamide [Example 1(n)] there was prepared N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(1-oxido-2-pyridiniomethoxy)benzamide, as a white solid, m.p. 264°C. [Elemental analysis:- C,52.51; H,3.53; N,9.74%. Calculated for $C_{19}H_{15}Cl_2N_3O_5$:- C,52.31; H,3.47; N,9.63%];

(r) By proceeding in a similar manner to Example 1(a) but using N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(pyridin-3-ylmethoxy)benzamide [Example 1(o)] there was prepared N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(1-oxido-3-pyridiniomethoxy)benzamide, as a white solid, m.p. 255°C.

(s) By proceeding in a similar manner to Example 1(a) but using N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(pyridin-4-ylmethoxy)benzamide [Example 1(p)] there was prepared N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(1-oxido-4-pyridiniomethoxy)benzamide, as a white solid, m.p. 212°C.

(t) By proceeding in a similar manner to Example 1(a) but using N-(3,5-dichloro-pyridin-4-yl)-4-methyl-3-(pyridin-2-ylethoxy)benzamide [Example 8(s)], and carrying out the reaction at ambient temperature, there was prepared N-(3,5-dichloropyridin-4-yl)-4-methyl-3-(1-oxido-2-pyridinioethoxy)benzamide, as a white solid, m.p. 202°C.

(u) By proceeding in a similar manner to Example 1(a) but using N-(3,5-dichloro-pyridin-4-yl)-4-methyl-3-(pyridin-2-ylethoxy)benzamide [Example 8(s)] there was prepared N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methyl-3-(1-oxido-2-pyridinioethoxy)benzamide, as a white solid, m.p. 153°C.

(u) By proceeding in a similar manner to Example 1(a) but using N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-{2-(1-piperidinyl)ethoxy}benzamide [Example 6(j)] there was prepared N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-{2-[1-(1-oxido-2-piperidinio)]ethoxy}benzamide, as a white solid, m.p. 136°C.

EXAMPLE 2

(a) N-(3,5-Dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(3-methyl-1,2,4-oxadiazol-5-ylmethoxy)benzamide

N-(3,5-Dichloropyridin-4-yl)-4-methoxy-3-(3-methyl-1,2,4-oxadiazol-5-ylmethoxy)benzamide [0.34g, Example 6(b)] was treated with peracetic acid (2.5ml, 32% in dilute acetic acid). The mixture was stirred at ambient temperature for 2.25 hours and then at 60°C for 45 minutes. The reaction mixture was cooled to ambient temperature, then diluted with water (20ml). The pH of the mixture was adjusted to 7 by addition of concentrated aqueous sodium hydroxide solution then solid sodium sulphite was added until the solution was negative to starch iodide paper. This mixture was extracted twice with ethyl acetate (20ml). The combined extracts were dried over magnesium sulphate and then evaporated. The residual yellow oil was subjected to flash chromatography on silica eluting with a mixture of dichloromethane and methanol (9:1, v/v). Fractions containing the required product were combined and then evaporated. The resulting solid was recrystallised from ethyl acetate affording the title compound (0.045g) as colourless crystals, m.p. 174-176°C. [Elemental analysis:- C,48.46; H,3.39; N,13.11%. Calculated:- C,48.07; H,3.32; N,13.17%].

(b) By proceeding in a similar manner to Example 2(a) but using N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-phenylethoxy)benzamide [Example 7(b)] there was prepared

N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(2-phenylethoxy)benzamide, which was recrystallised from a mixture of acetone and petroleum ether (b.p. 40-60°C) as a cream coloured solid, m.p. 188-194°C. [Elemental analysis:- C,58.3; H,4.3; N,6.4%. Calculated:- C,58.2; H,4.2; N,6.5%].

(c) By proceeding in a similar manner to Example 2(a) but using N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[2-(pyridin-2-yl)ethoxy]benzamide [Example 7(e)], and carrying out the reaction at ambient temperature, there was prepared N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[2-(1-oxido-2-pyridinio)ethoxy]benzamide as an off-white solid, m.p. 169°C. [Elemental analysis:- C,54.7; H,4.0; N,9.6%. Calculated for $C_{20}H_{17}Cl_2N_3O_4 \cdot 0.27H_2O$:- C,54.7; H,4.0; N,9.5%];

(d) By proceeding in a similar manner to Example 2(a) but using N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[2-(pyridin-2-yl)ethoxy]benzamide [Example 7(e)] there was prepared N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-[2-(1-oxido-2-pyridinio)ethoxy]benzamide as an off-white solid, m.p. 120-122°C. [Elemental analysis:- C,51.6; H,3.9; N,9.0%. Calculated for $C_{20}H_{17}Cl_2N_3O_5 \cdot 0.88H_2O$:- C,51.5; H,4.1; N,9.0%].

(e) By proceeding in a similar manner to Example 2(a) but using 3-benzyloxy-N-(3,5-dichloropyridin-4-yl)-4-methoxybenzamide [Example 6(f)] there was prepared 3-benzyloxy-N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxybenzamide which was recrystallised from acetonitrile as a white solid, m.p. 163-166°C. [Elemental analysis:- C,55.39; H,3.88; N,6.36%. Calculated for $C_{20}H_{16}Cl_2N_2O_3 \cdot H_2O$:- C,54.92; H,4.29; N,6.40%].

(f) By proceeding in a similar manner to Example 2(a) but using N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[3-(pyridin-3-

yl)propyloxy]benzamide [Example 6(h)] there was prepared N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-[3-(1-oxido-3-pyridinio)propyloxy]benzamide as colourless crystals, m.p. 181-182°C. [Elemental analysis:- C,54.16; H,4.21; N,9.14%. Calculated for $C_{21}H_{19}Cl_2N_3O_5$:- C,54.32; H,4.12; N,9.04%].

(g) By proceeding in a similar manner to Example 2(a) but using N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-[3-(pyridin-4-yl)propyloxy]benzamide [Example 8(g)] there was prepared N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-[3-(1-oxido-4-pyridinio)propyloxy]benzamide, which was recrystallised from aqueous ethanol as colourless crystals, m.p. 236-238°C. [Elemental analysis:- C,54.30; H,4.15; N,9.04%. Calculated for $C_{21}H_{19}Cl_2N_3O_5$:- C,54.32; H,4.12; N,9.04%].

EXAMPLE 3

N-(3,5-Dichloro-1-oxido-4-pyridinio)-4-difluoromethoxy-3-(2-phenylethoxy)benzamide

A solution of N-acetyl-N-(3,5-dichloro-1-oxido-4-pyridinio)-4-difluoromethoxy-3-[2-phenylethoxy]-benzamide (0.18g, Reference Example 16) and piperidine (0.1ml) in dry dimethylformamide (2ml) was stirred at ambient temperature for 40 minutes. The reaction mixture was then evaporated. The residual yellow oil was subjected to flash chromatography on silica gel, eluting with ethyl acetate, affording the title compound (0.069g) as colourless crystals, m.p. 141-144°C. [Elemental analysis:- C,54.1; H,3.5; N,5.8%. Calculated:- C,53.8; H,3.4; N,6.0%].

EXAMPLE 4

(a) 3-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-ylmethoxy]-N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxybenzamide

A stirred solution of N-(3,5-dichloro-1-oxido-4-pyridinio)acetamide (0.54g, Reference Example 14) in dimethylformamide (25ml) was treated with sodium hydride

(0.36g, 60% dispersion in mineral oil) under nitrogen. After stirring at ambient temperature for 1 hour, the mixture was treated with a solution of 3-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-ylmethoxy]-4-methoxybenzoyl chloride [0.96g, Reference Example 7(a)] in dry dichloromethane (25ml) whilst maintaining the temperature below 25°C. After stirring at ambient temperature for 4 hours the reaction mixture was left standing overnight then evaporated. The residue was treated with water (50ml) and the pH of the mixture was then adjusted to 4 by addition of concentrated hydrochloric acid. The resulting solid was recrystallised from methanol, with charcoal treatment, then recrystallised from a mixture of methanol and water affording the title compound (0.088g) as colourless crystals.

(b) By proceeding in a similar manner to Example 4(a) but using 4-methoxy-3-[2-(pyridin-3-yl)ethoxy]benzoyl chloride [(Reference Example 7(c)] there was prepared N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-[2-(pyridin-3-yl)ethoxy]benzamide as a white solid, m.p. 189-191°C. [Elemental analysis:- C,53.4; H,3.9; N,9.3%. Calculated for $C_{20}H_{17}Cl_2N_3O_4 \cdot 0.75H_2O$:- C,53.7; H,4.2; N,9.4%];

(c) By proceeding in a similar manner to Example 4(a) but using 4-difluoromethoxy-3-[2-(pyridin-2-yl)ethoxy]benzoyl chloride [Reference Example 7(e)] there was prepared N-(3,5-dichloro-1-oxido-4-pyridinio)-4-difluoromethoxy-3-[2-(pyridin-2-yl)ethoxy]benzamide which was recrystallised from a mixture of dichloromethane and diethyl ether as colourless crystals, m.p.147-149°C. [Elemental analysis:- C,50.8; H,3.2; N,8.7%. Calculated:- C,51.1; H,3.2; N,8.9%];

(d) By proceeding in a similar manner to Example 4(a) but using 4-methoxy-3-(benzylthiomethyl)benzoyl chloride [Reference

Example 7(o)] there was prepared 3-(benzylthiomethyl)-N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxybenzamide as a yellow solid, m.p.168-172°C. [Elemental analysis:- C,55.90; H,4.05; N,6.54%. Calculated:- C,56.08; H,4.00; N,6.24%];

EXAMPLE 5

(a) 3-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxybenzamide

A stirred solution of N-(3,5-dichloro-1-oxido-4-pyridinio)acetamide (0.5g, Reference Example 14) in dimethylformamide (200ml), under nitrogen, was treated with sodium hydride (0.28g, 60% dispersion in mineral oil) over a period of 15 minutes. The mixture was stirred at ambient temperature for 3 hours, then cooled to 0°C, then treated dropwise with a solution of 3-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]-4-methoxybenzoyl azide (prepared by treating a solution of 3-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]-4-methoxybenzoic acid [0.66g, reference Example 12(a)] and diphenylphosphoryl azide (0.47g) in dimethylformamide (400ml) with triethylamine (0.33ml) and stirring at ambient temperature for 3 hours) whilst maintaining the temperature at 0°C. After stirring at ambient temperature for 3 days the reaction mixture was evaporated to low volume and then treated with water (200ml). The mixture was extracted three times with dichloromethane (300ml). The combined extracts were evaporated. The residual orange oil was triturated with methanol. The insoluble white solid was recrystallised from a mixture of tetrahydrofuran and water affording the title compound (0.15g) as white needles, m.p. 290-291°C. [Elemental analysis:- C,50.3; H,2.93; N,10.61%. Calculated for $C_{21}H_{13}Cl_3N_4O_4 \cdot 0.75H_2O$:- C,49.9; H,2.89; N,11.08%];

(b) By proceeding in a similar manner to Example 5(a) but using 4-methoxy-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-

yl]benzoyl azide (prepared from 4-methoxy-3-[3-(4-methoxyphenyl)-1,2,4,-oxadiazol-5-yl]benzoic acid, Reference Example 12(b)) there was prepared N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]benzamide which was recrystallised from a mixture of tetrahydrofuran and methanol as a yellow solid, m.p. 267-268°C;

(c) By proceeding in a similar manner to Example 5(a) but using 4-methoxy-3-(3-phenyl-1,2,4-oxadiazol-5-yl)benzoyl azide (prepared from 4-methoxy-3-(3-phenyl-1,2,4-oxadiazol-5-yl)benzoic acid, Reference Example 12(c)) there was prepared N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(3-phenyl-1,2,4-oxadiazol-5-yl)benzamide which was recrystallised from tetrahydrofuran as a white solid, m.p. 269-270°C. [Elemental analysis:- C,55.07; H,3.18; N,12.09%. Calculated:- C,55.15; H,3.09; N,12.25%];

(d) By proceeding in a similar manner to Example 5(a) but using 4-methoxy-3-[3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl]benzoyl azide (prepared from 4-methoxy-3-[3-(pyridin-2-yl)1,2,4-oxadiazol-5-yl]benzoic acid, Reference Example 12(d)) there was prepared N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-[3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl]benzamide which was recrystallised from methanol as white crystals, m.p. 264-265°C;

(e) By proceeding in a similar manner to Example 5(a) but using 5-methoxy-4-(2-[4-methoxyphenyl]ethoxy)-pyridine-2-carboxylic acid azide (prepared from 5-methoxy-4-(2-[4-methoxyphenyl]ethoxy)pyridine-2-carboxylic acid, Reference Example 11(e)) there was prepared N-(3,5-dichloro-1-oxido-4-pyridinio)-5-methoxy-4-[2-(4-methoxyphenyl)ethoxy]pyridine-2-carboxamide which was recrystallised from aqueous ethanol as a

colourless solid, m.p. 181-182°C. [Elemental analysis:- C,54.5; H,4.13; N,8.98%. Calculated:- C,54.32;H,4.12;N,9.04%].

(f) By proceeding in a similar manner to Example 5(a) but using 4-methoxy-3-[2-(pyridin-2-yl)ethoxy]benzoyl azide (prepared from 4-methoxy-3-[2-(pyridin-2-yl)-ethoxy]benzoic acid, Reference Example 8(d)) there was prepared N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-[2-(pyridin-2-yl)ethoxy]benzamide as a white solid, m.p. 186-188°C. [Elemental analysis:- C,54.5; H,4.0; N,9.6%. Calculated for $C_{20}H_{17}Cl_2N_3O_4 \cdot 0.4H_2O$:- C,54.5; H,4.05; N,9.5%];

(g) By proceeding in a similar manner to Example 5(a) but using 5-methoxy-4-(2-[pyridin-3-yl]ethoxy)pyridine-2-carboxylic acid azide (prepared from 5-methoxy-4-(2-[pyridin-3-yl]ethoxy)pyridine-2-carboxylic acid, Reference Example 11(c)) there was prepared N-(3,5-dichloro-1-oxido-4-pyridinio)-5-methoxy-4-(2-[pyridin-3-yl]ethoxy)pyridine-2-carboxamide which was recrystallised from acetonitrile as off-white crystals, m.p. 204-205°C. [Elemental analysis:- C,52.5; H,3.8; N,13.1%. Calculated:- C,52.4; H,3.7; N,12.9%].

(h) By proceeding in a similar manner to Example 5(a) but using 5-methoxy-4-(2-[pyridin-2-yl]ethoxy)pyridine-2-carboxylic acid azide (prepared from 5-methoxy-4-(2-[pyridin-2-yl]ethoxy)pyridine-2-carboxylic acid, Reference Example 11(d)) there was prepared N-(3,5-dichloro-1-oxido-4-pyridinio)-5-methoxy-4-(2-[pyridin-2-yl]ethoxy)pyridine-2-carboxamide which was recrystallised from acetonitrile as colourless needles, m.p.168-170°C. [Elemental analysis:- C,52.3; H,3.7; N,13.0%. Calculated:- C,52.4; H,3.7 N,12.9%];

(i) By proceeding in a similar manner to Example 5(a) but using 3-[3-(pyridin-2-yl)-1,2,4-oxadiazol-5-ylmethoxy]-4-

methoxybenzoyl azide (prepared from 4-methoxy-3-[3-(pyridin-2-yl)-1,2,4-oxadiazol-5-ylmethoxy]benzoic acid, Reference Example 8(b)) there was prepared N-(3,5-dichloro-1-oxido-4-pyridinio)-3-[3-(pyridin-2-yl)-1,2,4-oxadiazol-5-ylmethoxy]-4-methoxybenzamide as colourless crystals, m.p. 140-150°C. [Elemental analysis:- C,51.66; H,3.10; N,14.34%. Calculated for $C_{21}H_{13}Cl_3N_4O_4 \cdot 0.75H_2O$:- C,51.83; H,3.15; N,14.43%];

(j) By proceeding in a similar manner to Example 5(a) but using 4-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-ylmethoxy]-5-methoxypyridine-2-carboxylic acid azide (prepared from 4-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-ylmethoxy]-5-methoxypyridine-2-carboxylic acid, Reference Example 11(a)) there was prepared 4-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-ylmethoxy]-N-(3,5-dichloro-1-oxido-4-pyridinio)-5-methoxypyridine-2-carboxamide which was recrystallised from n-butanol, with charcoal treatment as colourless crystals, m.p. 231-233°C. [Elemental analysis:- C,48.25; H,2.70; N,13.4%. Calculated:- C,48.57; H,2.72; N,13.25%].

(k) By proceeding in a similar manner to Example 5(a) but using 4-methoxy-3-[3-(pyridin-4-yl)propyloxy]benzoyl azide (prepared from 4-methoxy-3-[3-(pyridin-4-yl)propyloxy]benzoic acid, Reference Example 11(f)) there was prepared N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-[3-(pyridin-4-yl)propyloxy]benzamide which was recrystallised from ethyl acetate, with charcoal treatment, as colourless crystals, m.p. 169-170°C. [Elemental analysis:- C,56.24; H,4.28; N,9.32%. Calculated for $C_{21}H_{19}Cl_2N_3O_4$:- C,56.26; H,4.27; N,9.37%].

(l) By proceeding in a similar manner to Example 5(a) but using 4-methoxy-3-[3-(pyridin-3-yl)propyloxy]benzoyl azide (prepared from 4-methoxy-3-[3-(pyridin-3-yl)propyloxy]benzoic acid, Reference Example 11(g)) there was prepared

N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-[3-(pyridin-3-yl)propyloxy]benzamide which was recrystallised from ethyl acetate as cream coloured crystals, m.p. 169-170°C. [Elemental analysis:- C,56.56; H,4.35; N,9.37%. Calculated for $C_{21}H_{19}Cl_2N_3O_4$:- C,56.26; H,4.27; N,9.37%].

(m) By proceeding in a similar manner to Example 5(a) but using 4-methoxy-3-(pyridin-2-yloxymethyl)benzoyl azide (prepared from 4-methoxy-3-(pyridin-2-yloxymethyl)benzoic acid, Reference Example 11(j)) there was prepared N-(3,5-dichloro-1-oxido-4-pyridinio)-4-methoxy-3-(pyridin-2-yloxymethyl)benzamide as colourless crystals, m.p. 104-105°C. [Elemental analysis:- C,54.30; H,3.60; N,10.00%. Calculated for $C_{19}H_{15}Cl_2N_3O_4$:- C,53.76; H,3.39; N,10.42%].

EXAMPLE 6

(a) 3-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-ylmethoxy]-N-(3,5-dichloro-pyridin-4-yl)-4-methoxybenzamide

A stirred suspension of (3,5-dichloropyridin-4-yl)-N-[fluoro(3-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-ylmethoxy)-4-methoxyphenyl)methylene]amine [0.65g, Reference Example 1(a)] in tetrahydrofuran (50ml) was treated portionwise with potassium trimethylsilanoate (0.57g). The resulting yellow solution was stirred at ambient temperature for 3 hours. After standing at ambient temperature overnight the reaction mixture was evaporated. The residue treated with water (30ml). The insoluble material was dried at 60°C under vacuum affording a colourless solid (0.49g). A portion (0.2g) of this material was recrystallised from ethyl acetate affording the title compound (0.07g) as colourless crystals, m.p. 203-204°C. [Elemental analysis:- C,52.15; H,3.11; N,10.93%. Calculated:- C,52.25; H,2.99; N,11.08%].

(b) By proceeding in a similar manner to Example 6(a) but using (3,5-dichloropyridin-4-yl)-N-[fluoro(4-methoxy-3-(3-methyl-1,2,4-oxadiazol-5-ylmethoxy)phenyl)methylene]amine [Reference Example 1(b)] there was prepared N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(3-methyl-1,2,4-oxadiazol-5-ylmethoxy)benzamide, which was recrystallised from methanol as colourless crystals, m.p. 122-173°C. [Elemental analysis:- C,49.89; H,3.45; N,13.69%. Calculated:- C,50.24; H,3.56; N,13.84%].

(c) By proceeding in a similar manner to Example 6(a) but using (3,5-dichloropyridin-4-yl)-N-[fluoro-(4-methoxy-3-{2-pyridin-4-ylethoxy}phenyl)-methylene]amine [Reference Example 1(c)] there was prepared N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[2-(pyridin-4-yl)ethoxy]benzamide as a white solid, m.p. 145-147°C. [Elemental analysis:- C,57.68; H,4.14; N,9.86%. Calculated:- C,57.43; H,4.10; N,10.05%].

(d) By proceeding in a similar manner to Example 6(a) but using (3,5-dichloropyridin-4-yl)-N-[fluoro(4-methoxy-3-{2-(4-methylthiazol-5-yl)ethoxy}phenyl)methylene]amine [Reference Example 1(d)] there was prepared N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-{4-methylthiazol-5-yl}ethoxy)benzamide as a colourless solid, m.p. 188-189°C. [Elemental analysis:- C,52.6; H,4.0; N,9.7; S,7.3%. Calculated:- C,52.1; H,3.9; N,9.6; S,7.3%].

(e) By proceeding in a similar manner to Example 6(a) but using (3,5-dichloropyridin-4-yl)-N-[fluoro-(4-methoxy-3-{2-thien-2-ylethoxy}phenyl)-methylene]amine [Reference Example 1(e)] there was prepared N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-thien-2-ylethoxy)benzamide, which was recrystallised from ethyl acetate as a colourless solid, m.p.158-159°C. [Elemental analysis:- C,53.6; H,3.8; N,6.7; S,7.55%. Calculated:- C,55.9; H,3.8; N,6.6; S,7.6%].

(f) By proceeding in a similar manner to Example 6(a) but using (3,5-dichloropyridin-4-yl)-N-[fluoro-(4-methoxy-3-(benzyloxy)phenyl)-methylene]amine [Reference Example 1(f)] there was prepared N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-benzyloxybenzamide as a white solid, m.p.212-215°C.

(g) By proceeding in a similar manner to Example 6(a) but using (3,5-dichloropyridin-4-yl)-N-[fluoro-(4-methoxy-3-(4-phenylbutoxy)phenyl)-methylene]amine [Reference Example 1(g)] there was prepared N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(4-phenylbutoxy)benzamide, which was recrystallised from ethyl acetate as a colourless solid, m.p.163-164°C. [Elemental analysis:- C,62.03; H,4.98; N,6.29%. Calculated for $C_{23}H_{22}Cl_2N_2O_3$:- C,62.01; H,4.88; N,6.22%].

(h) By proceeding in a similar manner to Example 6(a) but using (3,5-dichloropyridin-4-yl)-N-[fluoro-(4-methoxy-3-((3-pyridin-3-yl)propyloxy)phenyl)-methylene]amine [Reference Example 1(h)] there was prepared N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[3-(pyridin-3-yl)propyloxy]benzamide as a colourless solid.

(i) By proceeding in a similar manner to Example 6(a) but using (3,5-dichloropyridin-4-yl)-N-[fluoro-(4-methoxy-3-(2-benzyloxyethoxy)phenyl)-methylene]amine [Reference Example 1(i)] there was prepared N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-benzyloxyethoxy)benzamide which was recrystallised from toluene, with charcoal treatment, as colourless crystals, m.p. 191-192°C. [Elemental analysis:- C,58.88; H,4.53; N,6.31%. Calculated for $C_{22}H_{20}Cl_2N_2O_4$:- C,59.07; H,4.51; N,6.26%].

(j) By proceeding in a similar manner to Example 6(a) but using (3,5-dichloropyridin-4-yl)-N-[fluoro-(4-methoxy-3-(2-

piperidinylethoxy)phenyl)-methylene]amine [Reference Example 1(j)] there was prepared N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-(1-piperidinyl)ethoxy)benzamide, which was recrystallised from acetonitrile, as white crystals, m.p. 170°C. [Elemental analysis:- C,56.56; H,5.58; N,10.10%. Calculated for $C_{20}H_{23}Cl_2N_3O_3$:- C,56.61; H,5.46; N,9.90%].

EXAMPLE 7

(a) 3-(2-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]ethyl)-N-(3,5-dichloropyridin-4-yl)-4-methoxybenzamide

A solution of 4-amino-3,5-dichloropyridine (0.51g, prepared as described in the specification of International Patent Application Publication No. WO92/12961) in dry dimethylformamide (40ml), under nitrogen, was treated with sodium hydride (0.26g), 60% dispersion in mineral oil). After stirring at ambient temperature for 30 minutes the mixture was treated dropwise with a solution of 3-(2-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]ethyl)-4-methoxybenzoyl chloride [1.19g, Reference Example 7(b)] in dry dichloromethane (25ml) whilst maintaining the temperature below 25°C. Stirring was continued at ambient temperature for 3 hours and the mixture was then left standing for 18 hours. The reaction mixture was evaporated. The residue treated with 1N hydrochloric acid (130ml). The resulting solid was washed with water, then dried and then recrystallised from acetonitrile affording the title compound (0.96g) as colourless crystals, m.p. 188-189°C. [Elemental analysis:- C,55.24; H,3.12; N,11.06%. Calculated:- C,54.84; H,3.40; N,11.12%].

(b) By proceeding in a similar manner to Example 7(a) but using 4-methoxy-3-(2-phenylethoxy)benzoyl chloride [Reference Example 7(f)], there was prepared N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(2-phenylethoxy)benzamide which was recrystallised from toluene as an off-white solid, m.p. 154-158°C. [Elemental

analysis:- C,60.6; H,4.4; N,6.5%. Calculated:- C,60.4; H,4.4; N,6.7%].

(c) By proceeding in a similar manner to Example 7(a) but using 4-difluoromethoxy-3-(2-phenylethoxy)benzoyl chloride [Reference Example 7(g)], there was prepared N-(3,5-dichloropyridin-4-yl)-4-difluoromethoxy-3-(2-phenylethoxy)benzamide as a colourless solid, m.p. 134-136°C. [Elemental analysis:- C,55.7; H,3.6; N,6.1%. Calculated:-C,55.7; H,3.7; N,6.2%].

(d) By proceeding in a similar manner to Example 7(a) but using 5-methoxy-4-(2-[4-methoxyphenyl]ethoxy)pyridine-2-carbonyl chloride [Reference Example 7(j)] there was prepared N-(3,5-dichloropyridin-4-yl)-5-methoxy-4-[2-(4-methoxyphenyl)ethoxy]pyridine-2-carboxamide which was recrystallised from ethyl acetate as a colourless solid, m.p. 151-152°C. [Elemental analysis:- C,56.13; H,4.39; N,9.44%. Calculated:- C,56.26; H,4.27; N,9.37%].

(e) By proceeding in a similar manner to Example 7(a) but using 4-methoxy-3-[2-(pyridin-2-yl)ethoxy]benzoyl chloride [Reference Example 7(d)] there was prepared N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[2-(pyridin-2-yl)ethoxy]benzamide as a white solid, m.p. 151-152°C. [Elemental analysis:- C,57.3; H,4.1; N,10.3%. Calculated:- C,57.4; H,4.1; N,10.1%];

(f) By proceeding in a similar manner to Example 7(a) but using 4-methoxy-3-[2-(pyridin-3-yl)ethoxy]benzoyl chloride [Reference Example 7(c)] there was prepared N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[2-(pyridin-3-yl)ethoxy]benzamide as a white solid, m.p. 159°C. [Elemental analysis:- C,57.4; H,4.1; N,10.1%. Calculated:- C,57.4; H,4.1; N,10.1%].

(g) By proceeding in a similar manner to Example 7(a) but using 4-methoxy-3-(2-phenylethyl)benzoyl chloride [Reference Example 7(k)] there was prepared N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-phenylethyl)benzamide, which was recrystallised from acetonitrile as white plates, m.p. 186-187°C. [Elemental analysis:- C,62.94; H,4.54; N,7.19%. Calculated for $C_{21}H_{18}Cl_2N_2O_2$:- C,62.86; H,4.52; N,6.98%].

(h) By proceeding in a similar manner to Example 7(a) but using 4-methoxy-3-(2-phenylethynyl)benzoyl chloride [Reference Example 7(l)] there was prepared N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-phenylethynyl)benzamide, which was recrystallised from acetonitrile as a white crystalline solid, m.p. 244-246°C. [Elemental analysis:- C,63.42; H,3.51; N,6.96%. Calculated for $C_{21}H_{14}Cl_2N_2O_2$:- C,63.49; H,3.55; N,7.05%].

(i) By proceeding in a similar manner to Example 7(a) but using 4-methoxy-3-(phenoxymethyl)benzoyl chloride [Reference Example 7(m)] there was prepared N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(phenoxymethyl)benzamide as a yellow solid, m.p. 139-140°C. [Elemental analysis:- C,59.57; H,4.00; N,6.95%. Calculated for $C_{20}H_{16}Cl_2N_2O_3$:- C,59.28; H,4.00; N,6.98%].

(j) By proceeding in a similar manner to Example 7(a) but using 4-methoxy-3-(benzyloxymethyl)benzoyl chloride [Reference Example 7(p)] there was prepared N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(benzyloxymethyl)benzamide which was recrystallised from ethyl acetate as colourless crystals, m.p. 142-143°C. [Elemental analysis:- C,60.45; H,4.35; N,6.71%. Calculated for $C_{21}H_{18}Cl_2N_2O_3$:- C,60.49; H,4.44; N,6.79%].

(k) By proceeding in a similar manner to Example 7(a) but using 4-methoxy-3-(4-methoxyphenyl)benzoyl chloride [Reference Example 7(n)] there was prepared N-(3,5-dichloropyridin-4-yl)-

4-methoxy-3-(4-methoxyphenyl)benzamide which was recrystallised from acetonitrile as a white crystalline solid, m.p. 195-196°C. [Elemental analysis:- C,59.46; H,3.98; N,6.95%. Calculated for $C_{20}H_{16}Cl_2N_2O_3$:- C,59.57; H,4.00; N,6.95%].

(l) By proceeding in a similar manner to Example 7(a) but using 4-methoxy-3-[3-(2-thienyl)-1,2,4-oxadiazol-5-yl]methoxybenzoyl chloride [Reference Example 7(r)] there was prepared N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[3-(2-thienyl)-1,2,4-oxadiazol-5-yl]methoxybenzamide which was recrystallised from ethyl acetate as a white crystalline solid, m.p. 213-215°C.

(m) By proceeding in a similar manner to Example 7(a) but using 4-methoxy-3-[2-(4-chlorophenyl)-1,3,4-oxadiazol-5-yl]methoxybenzoyl chloride [Reference Example 7(s)] there was prepared N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[2-(4-chlorophenyl)-1,3,4-oxadiazol-5-yl]methoxybenzamide as a cream solid, m.p. 219-221°C. [Elemental analysis:- C,52.25; H,3.10; N,11.20%. Calculated for $C_{22}H_{15}Cl_3N_4O_4$:- C,52.25; H,2.99; N,11.08%].

(n) By proceeding in a similar manner to Example 7(a) but using 4-methoxy-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]methoxybenzoyl chloride [Reference Example 7(t)] there was prepared N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]methoxybenzamide as a yellow semi-solid.

EXAMPLE 8

(a) 3-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-N-(3,5-dichloropyridin-4-yl)-4-methoxybenzamide

A stirred solution of 4-amino-3,5-dichloropyridine (0.59g, prepared as described in the specification of International Patent Application Publication No. WO 92/12961) in dry

dimethylformamide (40ml), under nitrogen, was treated portionwise with sodium hydride (0.432g, 60% dispersion in mineral oil) over 15 minutes. After stirring at ambient temperature for 2 hours the mixture was treated dropwise with a solution of 3-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]-4-methoxybenzoyl azide (prepared by treating a stirred solution of 3-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]-4-methoxybenzoic acid [1g, Reference Example 12(a)] in dimethylformamide (150ml) under nitrogen with diphenylphosphoryl azide (0.71ml) followed by triethylamine (0.5ml) and then stirring the mixture at ambient temperature for 2 hours) whilst maintaining the temperature below 0°C. After stirring at ambient temperature for 16 hours the reaction mixture was evaporated. The residual brown semi-solid was dissolved in water (200ml). The solution was extracted three times with dichloromethane (150ml). The combined organic extracts were washed with 1N hydrochloric acid, then dried over magnesium sulphate and then evaporated. The residual white solid was recrystallised from a mixture of tetrahydrofuran, methanol and acetonitrile to give the title compound (0.12g) as a white solid, m.p. 284-285°C. [Elemental analysis:- C,53.02; H,2.75; N,11.78%. Calculated:- C,51.79; H,2.78; N,11.41%];

(b) By proceeding in a similar manner to Example 8(a) but using 3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]-4-methoxybenzoyl azide (prepared from 3-[3-(4-methoxyphenyl-1,2,4-oxadiazol-5-yl]-4-methoxybenzoic acid, Reference Example 12(b)) there was prepared N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]benzamide recrystallised from a mixture of tetrahydrofuran and methanol as a white solid, m.p. 244-245°C. [Elemental analysis:- C,56.05; H,3.29; N,11.65%. Calculated:- C,56.07; H,3.42; N,11.89%];

(c) By proceeding in a similar manner to Example 8(a) but using 4-methoxy-3-(3-phenyl-1,2,4-oxadiazol-5-yl)benzoyl azide [prepared from 4-methoxy-3-(3-phenyl-1,2,4-oxadiazol-5-yl)benzoic acid, Reference Example 12(c)] there was prepared N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(3-phenyl-1,2,4-oxadiazol-5-yl)benzamide recrystallised from a mixture of tetrahydrofuran and methanol as a white solid, m.p. 249-251°C. [Elemental analysis:-C,56.54; H,3.03; N,12.23%. Calculated:-C,57.15; H,3.20; N,12.70%];

(d) By proceeding in a similar manner to Example 8(a) but using 3-[3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl]-4-methoxybenzoyl azide {prepared from 4-methoxy-3-[3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl]benzoic acid, Reference Example 12(d)} there was prepared N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl]benzamide recrystallised from acetonitrile as a white solid, m.p. 237-238°C.

(e) By proceeding in a similar manner to Example 8(a) but using 5-methoxy-4-(2-[pyridin-3-yl]-ethoxy)pyridine-2-carboxylic acid azide {prepared from 5-methoxy-4-(2-[pyridin-3-yl]-ethoxy)pyridine-2-carboxylic acid, Reference Example 11(c)} there was prepared N-(3,5-dichloropyridin-4-yl)-5-methoxy-4-(2-[pyridin-3-yl]ethoxy)pyridine-2-carboxamide which was recrystallised from ethyl acetate as colourless crystals, m.p. 149-151°C. [Elemental analysis:- C,54.49; H,3.88;N, 13.37%. Calculated:- C,54.43; H,3.85; N,13.36%];

(f) By proceeding in a similar manner to Example 7(a) but using 5-methoxy-4-(2-[pyridin-2-yl]ethoxy)pyridine-2-carboxylic acid azide {prepared from 5-methoxy-4-(2-[pyridin-2-yl]ethoxy)pyridine-2-carboxylic acid Reference Example 11(d)} there was prepared N-(3,5-dichloropyridin-4-yl)-5-methoxy-4-(2-[pyridin-2-yl]ethoxy)pyridine-2-carboxamide which was

recrystallised from ethyl acetate as colourless needles, m.p.156-158°C. [Elemental analysis:- C,54.1; H,3.8; N,13.3%. Calculated:- C,54.4; H,3.85; N,13.4%].

(g) By proceeding in a similar manner to Example 8(a) but using 4-methoxy-3-[3-(pyridin-4-yl)propyloxy]benzoyl azide (prepared from 4-methoxy-3-[3-(pyridin-4-yl)propyloxy]benzoic acid, Reference Example 11(f)) there was prepared N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-[3-(pyridin-4-yl)propyloxy]benzamide which was recrystallised from ethyl acetate, with charcoal treatment, as colourless crystals, m.p. 182-183°C.

(h) By proceeding in a similar manner to Example 8(a) but using 4-methoxy-3-[3-(pyridin-3-yl)propyloxy]benzoyl azide (prepared from 4-methoxy-3-[3-(pyridin-3-yl)propyloxy]benzoic acid, Reference Example 11(g)) there was prepared N-(3,5-dichloro-pyridin-3-yl)-4-methoxy-3-[3-(pyridin-4-yl)propyloxy]benzamide which was recrystallised from ethyl acetate, with charcoal treatment, as colourless crystals, m.p. 171-172°C.

(i) By proceeding in a similar manner to Example 8(a) but using 4-methoxy-3-[2-(4-methoxyphenyl)ethenyl]benzoyl azide (prepared from 4-methoxy-3-[2-(4-methoxyphenyl)ethenyl]benzoic acid, Reference Example 12(e)) there was prepared N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-[2-(4-methoxyphenyl)ethenyl]benzamide which was recrystallised from methanol as white needles.

(j) By proceeding in a similar manner to Example 8(a) but using 4-methoxy-3-[2-(pyridin-2-yl)ethynyl]benzoyl azide (prepared from 4-methoxy-3-[2-(pyridin-2-yl)ethynyl]benzoic

acid, Reference Example 8(i)} there was prepared N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-[2-(pyridin-2-yl)ethynyl]benzamide which was recrystallised from acetonitrile, as a white crystalline solid, m.p. 211-212°C. [Elemental analysis:- C,60.34; H,3.31; N,10.64%. Calculated for $C_{20}H_{13}Cl_2N_3O_2$:- C,60.32; H,3.29; N,10.55%].

(k) By proceeding in a similar manner to Example 8(a) but using 4-methoxy-3-[2-(pyridin-2-yl)ethyl]benzoyl azide (prepared from 4-methoxy-3-[2-(pyridin-2-yl)ethyl]benzoic acid, Reference Example 19(b)} there was prepared N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-[2-(pyridin-2-yl)ethyl]benzamide which was recrystallised from diethyl ether, as a white crystalline solid, m.p. 166-167°C. [Elemental analysis:- C,60.07; H,4.31; N,10.63%. Calculated for $C_{20}H_{17}Cl_2N_3O_2$:- C,59.71; H,4.26; N,10.45%].

(l) By proceeding in a similar manner to Example 8(a) but using 4-methoxy-3-(2-naphthyl)benzoyl azide (prepared from 4-methoxy-3-(2-naphthyl)benzoic acid, Reference Example 25(a)} there was prepared N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(2-naphthyl)benzamide, which was recrystallised from aqueous methanol as a white solid, m.p. 192-193°C. [Elemental analysis:- C,65.26; H,3.81; N,6.62%. Calculated for $C_{23}H_{16}Cl_2N_2O_2$:- C,65.53; H,4.18; N,6.94%].

(m) By proceeding in a similar manner to Example 8(a) but using 4-methoxy-3-(2-benzofuranyl)benzoyl azide (prepared from 4-methoxy-3-(2-benzofuranyl)benzoic acid, Reference Example 25(b)} there was prepared N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(2-benzofuranyl)benzamide, which was recrystallised from a mixture of methanol and ethanol as an off-white solid, m.p. 199-200°C.

(n) By proceeding in a similar manner to Example 8(a) but using 4-methoxy-3-(1-naphthyl)benzoyl azide {prepared from 4-methoxy-3-(1-naphthyl)benzoic acid, Reference Example 25(c)} there was prepared N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(1-naphthyl)benzamide, which was recrystallised from ethanol, m.p. 190-191°C. [Elemental analysis:- C,65.58; H,3.99; N,6.78%. Calculated for $C_{20}H_{17}Cl_2N_3O_2$:- C,65.26; H,3.81; N,6.62%].

(o) By proceeding in a similar manner to Example 8(a) but using 4-methoxy-3-(3-thienyl)benzoyl azide {prepared from 4-methoxy-3-(3-thienyl)benzoic acid, Reference Example 25(d)} there was prepared N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(3-thienyl)benzamide, which was recrystallised from acetonitrile as white needles, m.p. 205-206°C. [Elemental analysis:- C,53.46; H,3.07; N,7.39%. Calculated for $C_{17}H_{12}Cl_2N_2O_2S$:- C,53.83; H,3.19; N,7.39%].

(p) By proceeding in a similar manner to Example 8(a) but using 4-methoxy-3-(pyridin-2-ylmethoxy)benzoyl azide {prepared from 4-methoxy-3-(pyridin-2-ylmethoxy)benzoic acid, Reference Example 11(k)} there was prepared N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(pyridin-2-ylmethoxy)benzamide, which was recrystallised from ethyl acetate as white crystals, m.p. 193°C. [Elemental analysis:- C,56.51; H,3.63; N,10.16%. Calculated for $C_{19}H_{15}Cl_2N_3O_3$:- C,56.46; H,3.74; N,10.39%].

(q) By proceeding in a similar manner to Example 8(a) but using 4-methoxy-3-(pyridin-3-ylmethoxy)benzoyl azide {prepared from 4-methoxy-3-(pyridin-3-ylmethoxy)benzoic acid, Reference Example 11(l)} there was prepared N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(pyridin-3-ylmethoxy)benzamide as a white solid, m.p. 173°C. [Elemental analysis:- C,56.54; H,3.76;

N,10.26%. Calculated for $C_{19}H_{15}Cl_2N_3O_3$:- C,56.46; H,3.74; N,10.39%].

(r) By proceeding in a similar manner to Example 8(a) but using 4-methoxy-3-(pyridin-4-ylmethoxy)benzoyl azide (prepared from 4-methoxy-3-(pyridin-4-ylmethoxy)benzoic acid, Reference Example 11(m)) there was prepared N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(pyridin-4-ylmethoxy)benzamide as a white solid, m.p. 184°C. [Elemental analysis:- C,56.38; H,3.75; N,10.33%. Calculated for $C_{19}H_{15}Cl_2N_3O_3$:- C,56.46; H,3.74; N,10.39%].

(s) By proceeding in a similar manner to Example 8(a) but using 4-methyl-3-(pyridin-2-ylethoxy)benzoyl azide (prepared from 4-methyl-3-(pyridin-2-ylethoxy)benzoic acid, Reference Example 11(n)) there was prepared N-(3,5-dichloro-pyridin-4-yl)-4-methyl-3-(pyridin-2-ylethoxy)benzamide as a white solid, m.p. 151°C. [Elemental analysis:- C,59.40; H,4.37; N,10.50%. Calculated for $C_{20}H_{17}Cl_2N_3O_2$:- C,59.71; H,4.26; N,10.46%].

EXAMPLE 9

2-(3,5-Dichloropyridin-4-yl)-1-{4-methoxy-3-[2-(pyridin-2-yl)ethoxy]phenyl}ethanone

A stirred solution of lithium diisopropylamide (17.5 mmoles) in dried tetrahydrofuran (30ml), under nitrogen, at -75°C, was treated with a solution of 3,5-dichloro-4-methylpyridine in dry tetrahydrofuran (5ml). After stirring for 1 hour at -75°C, the mixture was treated with a solution of methyl 4-methoxy-3-[2-(pyridin-2-yl)ethoxy]benzoate (2.28g, Reference Example 17) in dry tetrahydrofuran (5ml). After stirring at -75°C for 1 hour, the mixture was allowed to warm to room temperature, and then

treated with saturated aqueous ammonium chloride solution. The mixture was extracted with ethyl acetate (200ml). The organic phase was washed twice with water (100ml), then dried over magnesium sulphate, then evaporated. The residual oil was subjected to flash column chromatography on silica gel, eluting with ethyl acetate, to give a white solid (1.16g). A sample (0.2g) of this solid was subjected to reverse phase high pressure liquid chromatography (Dynamax-60Å C_{18} column), eluting with aqueous methanol (70% v/v), affording the title compound (0.13g) as a white solid, m.p. 133-135°C. [Elemental analysis:- C,59.9; H,4.35; N,6.52%. Calculated:- C,60.45; H,4.35; N,6.71%].

EXAMPLE 10

2-(3,5-Dichloropyridin-4-yl)-1-[4-methoxy-3-[2-(pyridin-3-yl)ethoxy]phenyl]ethanone

A solution of oxalyl chloride (0.4ml) in dry dichloromethane (20ml), under nitrogen, at -65°C, was treated dropwise with dimethyl sulphoxide (0.57ml). After stirring for 15 minutes, the mixture was treated with a solution of 2-(3,5-dichloropyridin-4-yl)1-[4-methoxy-3-[2-(pyridin-3-yl)ethoxy]phenyl]ethanol (1.6g, Reference Example 18) in dry dichloromethane (30ml) during 30 minutes. Stirring was continued at -65°C for 15 minutes, and then the mixture was treated dropwise with triethylamine (2.55ml). After 15 minutes, the reaction mixture was allowed to warm to room temperature and stirring was continued for 1 hour. The mixture was treated with water and then extracted three times with dichloromethane (100ml). The combined extracts were dried over magnesium sulphate and then evaporated. The residue was subjected to flash column chromatography on silica gel, eluting with ethyl acetate. The resulting white solid was subjected to reverse phase high pressure liquid chromatography (Dynamax-60Å C_{18} column), eluting with a mixture of methanol and water (7:3,

v/v), affording the title compound (0.16g) as a white solid, m.p. 135-136°C. [Elemental analysis:- C,59.5; H,4.3; N,6.4%. Calculated for $C_{21}H_{18}Cl_2N_2O_3 \cdot 0.3H_2O$:- C,59.7; H,4.4; N,6.6%].

REFERENCE EXAMPLE 1

(a) (3-5-Dichloropyridin-4-yl)-N-[fluoro(3-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-ylmethoxy)-4-methoxyphenyl)methylenelamine

A stirred solution of 5-[(3,5-dichloropyridin-4-ylimino)fluoromethyl]-2-methoxyphenol (0.67g, Reference Example 2), 3-(4-chlorophenyl)-5-hydroxymethyl-1,2,4-oxadiazole [0.45g, Reference Example 4(a)] and triphenylphosphine (0.67g) in dry tetrahydrofuran (50ml) was treated dropwise with a solution of diisopropylazodicarboxylate (0.46ml) in dry tetrahydrofuran (15ml) over 1 hour. After stirring at ambient temperature for 3 hours the reaction mixture was heated to reflux and then triphenyl phosphine (0.67g) was added. The mixture was then treated dropwise with a solution of diisopropylazodicarboxylate (0.46ml) in dry tetrahydrofuran (15ml) over 2 hours. After heating at reflux for 3.5 hours the reaction mixture was left at ambient temperature for 3 days and then evaporated. The residual solid was triturated with methanol affording the title compound (0.47g) as a colourless solid. The methanol soluble material was subjected to flash chromatography on silica eluting with ethyl acetate to give a further quantity of the title compound (0.18g).

(b) By proceeding in a similar manner to Reference Example 1(a) but using 5-hydroxymethyl-3-methyl-1,2,4-oxadiazole [Reference Example 4(b)] there was prepared (3-5-dichloropyridin-4-yl)-N-[fluoro(4-methoxy-3-(3-methyl-1,2,4-oxadiazol-5-ylmethoxy)phenyl)methylenelamine as an orange oil.

(c) By proceeding in a similar manner to Reference Example 1(a) but using 4-(2-hydroxyethyl)pyridine there was prepared (3,5-dichloropyridin-4-yl)-N-[fluoro-(4-methoxy-3-(2-pyridin-4-ylethoxy)phenyl)methylene]amine as a yellow oil, which solidified on standing.

(d) By proceeding in a similar manner to Reference Example 1(a) but using 2-(4-methyl-thiazol-5-yl)ethanol there was prepared (3,5-dichloropyridin-4-yl)-N-[fluoro-(4-methoxy-3-(2-(4-methylthiazol-5-yl)ethoxy)phenyl)methylene]amine as a white crystalline solid, m.p.122-123°C. [Elemental analysis:- C,52.2; H,3.6; N,9.4%; Calculated:- C,51.8; H,3.7; N,9.5%].

(e) By proceeding in a similar manner to Reference Example 1(a) but using 2-(2-thienyl)ethanol there was prepared (3,5-dichloropyridin-4-yl)-N-[fluoro-(4-methoxy-3-(2-thien-2-ylethoxy)phenyl)methylene]amine as a white solid, m.p.94-95°C. [Elemental analysis:- C,53.5; H,3.6; N,6.5; S,7.7%. Calculated:- C,53.7; H,3.55; N,6.6; S,7.5%].

(f) By proceeding in a similar manner to Reference Example 1(a) but using benzyl alcohol there was prepared (3,5-dichloropyridin-4-yl)-N-[fluoro-(4-methoxy-3-(benzyloxy)phenyl)-methylene]amine as a yellow solid, m.p.94-95°C.

(g) By proceeding in a similar manner to Reference Example 1(a) but using 4-phenyl-1-butanol there was prepared (3,5-dichloropyridin-4-yl)-N-[fluoro-(4-methoxy-3-(4-phenylbutoxy)phenyl)methylene]amine as a thick yellow oil.

(h) By proceeding in a similar manner to Reference Example 1(a) but using 3-pyridinepropanol there was prepared (3,5-dichloropyridin-4-yl)-N-[fluoro-(4-methoxy-3-((3-pyridin-

3-yl)propyloxy)phenyl)-methylene]amine as an orange coloured solid.

(i) By proceeding in a similar manner to Reference Example 1(a) but using 2-benzyloxyethanol there was prepared (3,5-dichloropyridin-4-yl)-N-[fluoro-(4-methoxy-3-(2-benzyloxyethoxy)phenyl)-methylene]amine as a colourless solid.

(j) By proceeding in a similar manner to Reference Example 1(a) but using 1-piperidine ethanol there was prepared (3,5-dichloropyridin-4-yl)-N-[fluoro-(4-methoxy-3-(2-(1-piperidinyl)ethoxy)phenyl)-methylene]amine as a yellow oil. [Elemental analysis:- C,56.52; H,5.31; N,9.71%. Calculated for $C_{20}H_{22}Cl_2FN_3O_2$:- C,56.34; H,5.20; N,9.86%].

REFERENCE EXAMPLE 2

5-[(3,5-Dichloropyridin-4-ylimino)fluoromethyl]-2-methoxyphenol

A stirred suspension of N-(3,5-dichloropyridin-4-yl)-3-hydroxy-4-methoxybenzamide (1.6g, Reference Example 3) in dry dichloromethane (100ml), under nitrogen, was treated with diethylaminosulphur trifluoride (2ml). The mixture was left to stand at ambient temperature overnight, then was washed twice with water (50ml), then washed with brine (50ml), then dried over magnesium sulphate, and then evaporated. The residue was triturated with ethyl acetate, to give the title compound as a pale yellow solid (0.95g), m.p. 163-165°C.

REFERENCE EXAMPLE 3

N-(3,5-Dichloropyridin-4-yl)-3-hydroxy-4-methoxybenzamide

A mixture of aluminium chloride (12.5g) and dry dichloromethane (150ml), under nitrogen, was stirred vigorously for 2 hours, then treated dropwise with a solution of 3-cyclopentyloxy-N-(3,5-dichloropyridin-4-yl)-4-methoxybenzamide (5.0g, prepared as described in the specification of International Patent

Application Publication No. WO 92/12961) in dry dichloromethane (60ml). The mixture was stirred at ambient temperature for 2 hours, then treated cautiously with water (12ml) and then stirred for a further period of 0.5 hours. The resulting solid was triturated five times with ethyl acetate (500ml), with stirring for 0.5 hours each time. The combined ethyl acetate solutions were evaporated to give the title compound (3.05g) as a buff solid.

REFERENCE EXAMPLE 4

(a) 3-(4-Chlorophenyl)-5-hydroxymethyl-1,2,4-oxadiazole

A mixture of 5-acetoxymethyl-3-(4-chlorophenyl)-1,2,4-oxadiazole [2.6g, Reference Example 5(a)], aqueous potassium carbonate (1.41g in 20ml water) and methanol (180ml) was stirred at ambient temperature for 1.25 hours. The reaction mixture was evaporated. The residue was treated with water. The insoluble material was dried and recrystallised from cyclohexane affording the title compound (1g) as colourless needles, m.p. 94-97°C.

(b) By proceeding in a similar manner to reference Example 4(a) but using 5-acetoxymethyl-3-methyl-1,2,4-oxadiazole (Reference Example 5(i)) there was prepared 5-hydroxymethyl-3-methyl-1,2,4-oxadiazole as a white solid.

(c) By proceeding in a similar manner to reference Example 4(a) but using 5-acetoxymethyl-3-(pyridin-2-yl)-1,2,4-oxadiazole [Reference Example 5(b)] there was prepared 5-hydroxymethyl-3-(pyridin-2-yl)-1,2,4-oxadiazole as cream coloured crystals, m.p. 143-145°C.

(d) By proceeding in a similar manner to reference Example 4(a) but using 5-acetoxymethyl-3-(2-thienyl)-1,2,4-oxadiazole [Reference Example 5(h)] there was prepared 5-hydroxymethyl-3-(2-thienyl)-1,2,4-oxadiazole as a brown semi-solid.

(e) By proceeding in a similar manner to reference Example 4(a) but using 5-acetoxymethyl-2-(4-chlorophenyl)-1,3,4-oxadiazole [Reference Example 32] there was prepared 5-hydroxymethyl-2-(4-chlorophenyl)-1,3,4-oxadiazole as a brown semi-solid.

(f) By proceeding in a similar manner to reference Example 4(a) but using 5-acetoxymethyl-3-(4-methoxyphenyl)-1,2,4-oxadiazole [Reference Example 5(j)] there was prepared 5-hydroxymethyl-3-(4-methoxyphenyl)-1,2,4-oxadiazole which was recrystallised from methanol as cream coloured crystals, m.p. 154-156°C.

REFERENCE EXAMPLE 5

(a) 5-Acetoxymethyl-3-(4-chlorophenyl)-1,2,4-oxadiazole

A stirred solution of 4-chlorophenylamidoxime (4.5g) in pyridine (20ml), under nitrogen, was treated dropwise with acetoxyacetyl chloride (6ml) with ice-water cooling to maintain the reaction temperature below 25°C. The mixture was heated at 90°C for 2 hours then evaporated. The black oily residue was treated portionwise with diethyl ether (200ml). The combined extracts were dried over magnesium sulphate and charcoal, and then evaporated. The residual yellow oil was filtered through a pad of silica eluting with dichloromethane. Evaporation of the filtrate gave the title compound (5.12g) as a colourless solid, m.p. 55-59°C.

(b) By proceeding in a similar manner to reference Example 5(a) but using pyridin-2-ylamidoxime there was prepared 5-acetoxymethyl-3-(pyridin-2-yl)-1,2,4-oxadiazole as a yellow oil.

(c) By proceeding in a similar manner to reference Example 5(a) but using 3-(5-methoxycarbonyl-2-methoxyphenyl)propionyl chloride [Reference Example 7(h)] there was prepared methyl 3-[2-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]ethyl]-4-methoxybenzoate as an orange coloured oily solid.

(d) By proceeding in a similar manner to reference Example 5(a) but using 5-methoxycarbonyl-2-methoxybenzoyl chloride [Reference Example 7(i)] there was prepared methyl 3-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]-4-methoxybenzoate as a cream coloured solid.

(e) By proceeding in a similar manner to Reference Example 5(a) but using 4-methoxyphenyl amidoxime and 5-methoxycarbonyl-2-methoxybenzoyl chloride [Reference Example 7(i)] there was prepared methyl 3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]-4-methoxybenzoate recrystallised from methanol as a white solid m.p. 184-185°C. [Elemental analysis:- C,63.64; H,4.73; N,8.27%. Calculated:- C,63.52; H,4.74; N,8.23%].

(f) By proceeding in a similar manner to Reference Example 5(a) but using benzamidoxime and 5-methoxycarbonyl-2-methoxybenzoyl chloride [Reference Example 7(i)] there was prepared methyl 3-(3-phenyl-1,2,4-oxadiazol-5-yl)-4-methoxybenzoate as a white solid, m.p. 178-180°C.

(g) By proceeding in a similar manner to Reference Example 5(a) but using pyridin-2-ylamidoxime and 5-methoxycarbonyl-2-methoxybenzoyl chloride [Reference Example 7(i)] there was prepared methyl 3-[3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl]-4-methoxybenzoate as a brown solid, m.p. 203-204°C. [Elemental analysis:- C,61.35; H,4.08; N,13.28%. Calculated:- C,61.73; H,4.21; N,13.50%].

(h) By proceeding in a similar manner to Reference Example 5(a) but using 2-thienylamidoxime [Reference Example 6(a)] there was prepared 5-acetoxymethyl-3-(2-thienyl)-1,2,4-oxadiazole as an orange oil.

(i) By proceeding in a similar manner to Reference Example 5(a) but using methylamidoxime [Reference Example 6(b)] there was prepared 5-acetoxymethyl-3-methyl-1,2,4-oxadiazole as a white oily solid.

(j) By proceeding in a similar manner to Reference Example 5(a) but using 4-methoxyphenylamidoxime [Reference Example 6(c)] there was prepared 5-acetoxymethyl-3-(4-methoxyphenyl)-1,2,4-oxadiazole as a white oily solid.

REFERENCE EXAMPLE 6

(a) 2-Thienylamidoxime

A stirred mixture of 2-thiophenecarbonitrile (10g) and hydroxylamine hydrochloride (7.7) in ethanol (300ml) was treated with sodium hydroxide (4.2g) in water (78ml) and the mixture was then heated at reflux for 6 hours. After standing at ambient temperature for 2 days then refluxing for a further 6 hours the reaction mixture was evaporated. The residual cream solid was treated with water (200ml) and the mixture extracted with a mixture of dichloromethane and ethyl acetate (250ml, 4:1, v/v) then twice with ethyl acetate (100ml and 50ml). The combined extracts were dried over magnesium sulphate then evaporated to give the title compound (12.1g) as a cream coloured solid which was used without further purification.

(b) By proceeding in a similar manner to Reference Example 6(a) but using acetonitrile there was prepared methylamidoxime as a white oily solid.

(c) By proceeding in a similar manner to Reference Example 6(a) but using 4-methoxybenzonitrile there was prepared 4-methoxyphenylamidoxime as a white solid.

REFERENCE EXAMPLE 7

(a) 3-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-ylmethoxy]-4-methoxybenzoyl chloride

A suspension of 3-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-ylmethoxy]-4-methoxybenzoic acid [0.92g, Reference Example 8(a)] in dichloromethane (50ml) was treated dropwise with oxalyl chloride (0.24ml). The yellow solution was stirred under nitrogen for 1.5 hours and then evaporated. Dry dichloromethane was added to the residue and then the mixture was evaporated affording the title compound (0.96g) as a yellow solid.

(b) By proceeding in a similar manner to Reference Example 7(a) but using 3-{2-[3-(4-chlorophenyl-1,2,4-oxadiazol-5-yl]ethyl}-4-methoxybenzoic acid [Reference Example 11(b)] and adding 1 drop of dimethyl formamide to the reaction mixture, there was prepared 3-{2-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]ethyl}-4-methoxybenzoyl chloride as a yellow solid;

(c) By proceeding in a similar manner to Reference Example 7(a) but using 4-methoxy-3-[2-(pyridin-3-yl)ethoxy]benzoic acid [Reference Example 8(c)] there was prepared 4-methoxy-3-[2-(pyridin-3-yl)ethoxy]benzoyl chloride as a pale yellow solid.

(d) By proceeding in a similar manner to Reference Example 7(a) but using 4-methoxy-3-[2-(pyridin-2-yl)ethoxy]benzoic acid [Reference Example 8(d)], and adding 3 drops of dimethylformamide to the reaction mixture, there was prepared 4-methoxy-3-[2-(pyridin-2-yl)ethoxy]benzoyl chloride as a pale yellow solid.

(e) By proceeding in a similar manner to Reference Example 7(a) but using 4-difluoromethoxy-3-[2-(pyridin-2-yl)ethoxy]benzoic acid [Reference Example 8(e)] there was prepared 4-difluoromethoxy-3-[2-(pyridin-2-yl)ethoxy]benzoyl chloride as a pale brown solid.

(f) By proceeding in a similar manner to Reference Example 7(a) but using 4-methoxy-3-(2-phenyl-ethoxy)benzoic acid [Reference Example 8(f)] there was prepared 4-methoxy-3-(2-phenylethoxy)benzoyl chloride as a yellow solid.

(g) By proceeding in a similar manner to Reference Example 7(a) but using 4-difluoromethoxy-3-(2-phenylethoxy)benzoic acid [0.6g, Reference Example 8(g)], and adding 1 drop of dimethyl formamide to the reaction mixture, there was prepared 4-difluoromethoxy-3-(2-phenylethoxy)benzoyl chloride as a pale yellow oil.

(h) By proceeding in a similar manner to Reference Example 7(a) but using 3-(5-methoxycarbonyl-2-methoxyphenyl)propionic acid [Reference Example 19(a)] and adding 1 drop of dimethyl formamide to the reaction mixture, there was prepared 3-(5-methoxycarbonyl-2-methoxyphenyl)propionyl chloride as a pale yellow oily solid;

(i) By proceeding in a similar manner to Reference Example 7(a) but using 2-methoxy-5-methoxycarbonylbenzoic acid [Reference Example 8(h)] and adding 1 drop of dimethyl formamide to the reaction mixture, there was prepared 5-methoxycarbonyl-2-methoxybenzoyl chloride as a pale yellow solid.

(j) By proceeding in a similar manner to reference Example 7(a) but using 5-methoxy-4-(2-[4-methoxyphenyl]ethoxy)pyridine-2-carboxylic acid [Reference Example 11(e)] there was prepared

5-methoxy-4-(2-[4-methoxyphenyl]ethoxy)pyridine-2-carbonyl chloride.

(k) By proceeding in a similar manner to reference Example 7(a) but using 4-methoxy-3-(2-phenylethyl)benzoic acid [Reference Example 19(c)], and adding 2 drops of dimethylformamide to the reaction mixture, there was prepared 4-methoxy-3-(2-phenylethyl)benzoyl chloride.

(l) By proceeding in a similar manner to reference Example 7(a) but using 4-methoxy-3-(2-phenylethynyl)benzoic acid [Reference Example 8(j)], and adding 2 drops of dimethylformamide to the reaction mixture, there was prepared 4-methoxy-3-(2-phenylethynyl)benzoyl chloride.

(m) By proceeding in a similar manner to reference Example 7(a) but using 4-methoxy-3-(phenoxymethyl)benzoic acid [Reference Example 11(h)] there was prepared 4-methoxy-3-(phenoxymethyl)benzoyl chloride.

(n) By proceeding in a similar manner to reference Example 7(a) but using 4-methoxy-3-(4-methoxyphenyl)benzoic acid [Reference Example 25(e)], and adding 3 drops of dimethylformamide to the reaction mixture, there was prepared 4-methoxy-3-(4-methoxyphenyl)benzoyl chloride.

(o) By proceeding in a similar manner to Reference Example 7(a) but using 4-methoxy-3-(benzylthiomethyl)benzoic acid [Reference Example 12(f)], and adding 1 drop of dimethylformamide to the reaction mixture, there was prepared 4-methoxy-3-(benzylthiomethyl)benzoyl chloride.

(p) By proceeding in a similar manner to Reference Example 7(a) but using 4-methoxy-3-(benzyloxymethyl)benzoic acid

[Reference Example 11(i)], and adding 1 drop of dimethylformamide to the reaction mixture, there was prepared 4-methoxy-3-(benzyloxymethyl)benzoyl chloride as colourless crystals.

(r) By proceeding in a similar manner to Reference Example 7(a) but using 4-methoxy-3-[3-(2-thienyl)-1,2,4-oxadiazol-5-yl]methoxybenzoic acid [Reference Example 8(k)], and adding 2 drops of dimethylformamide to the reaction mixture, there was prepared 4-methoxy-3-[3-(2-thienyl)-1,2,4-oxadiazol-5-yl]methoxybenzoyl chloride

(s) By proceeding in a similar manner to Reference Example 7(a) but using 4-methoxy-3-[2-(4-chlorophenyl)-1,3,4-oxadiazol-5-yl]methoxybenzoic acid [Reference Example 8(l)], and adding 2 drops of dimethylformamide to the reaction mixture, there was prepared 4-methoxy-3-[2-(4-chlorophenyl)-1,3,4-oxadiazol-5-yl]methoxybenzoyl chloride as a yellow solid.

(t) By proceeding in a similar manner to Reference Example 7(a) but using 4-methoxy-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]methoxybenzoic acid [Reference Example 8(m)], and adding 2 drops of dimethylformamide to the reaction mixture, there was prepared 4-methoxy-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]methoxybenzoyl chloride as a yellow solid.

REFERENCE EXAMPLE 8

(a) 3-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-ylmethoxy]-4-methoxybenzoic acid

A stirred suspension of 3-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-ylmethoxy]-4-methoxybenzaldehyde [1.45g, Reference Example 9(a)] and sulphamic acid (0.86g) in glacial acetic acid (15ml) was treated dropwise with a solution of sodium chlorite (0.76g) in water (15ml). The reaction mixture was stirred at ambient temperature for 1 hour then diluted with ice-water. The

insoluble material was washed with water and then dried affording the title compound (1.0g) as a colourless solid, m.p. 210-215°C with decomposition.

(b) By proceeding in a similar manner to Reference Example 8(a) but using 4-methoxy-3-[3-(pyridin-2-yl)-1,2,4-oxadiazol-5-ylmethoxy]benzaldehyde [Reference Example 9(b)] there was prepared 4-methoxy-3-[3-(pyridin-2-yl)-1,2,4-oxadiazol-5-ylmethoxy]benzoic acid as a white solid.

(c) By proceeding in a similar manner to Reference Example 8(a) but using 4-methoxy-3-[2-(pyridin-3-yl)ethoxy]benzaldehyde [Reference Example 9(c)] there was prepared 4-methoxy-3-[2-(pyridin-3-yl)ethoxy]benzoic acid as a white solid, m.p. 189°C.

(d) By proceeding in a similar manner to Reference Example 8(a) but using 4-methoxy-3-[2-(pyridin-2-yl)ethoxy]benzaldehyde [Reference Example 9(d)] there was prepared 4-methoxy-3-[2-(pyridin-2-yl)ethoxy]benzoic acid as an off-white solid.

(e) By proceeding in a similar manner to Reference Example 8(a) but using but using 4-difluoromethoxy-3-[2-(pyridin-2-yl)ethoxy]benzaldehyde [Reference Example 9(e)] there was prepared 4-difluoromethoxy-3-[2-(pyridin-2-yl)ethoxy]benzoic acid as an off-white solid.

(f) By proceeding in a similar manner to Reference Example 8(a) but using 4-methoxy-3-(2-phenyl-ethoxy)benzaldehyde [Reference Example 10(a)] there was prepared 4-methoxy-3-(2-phenylethoxy)benzoic acid as a cream solid.

(g) By proceeding in a similar manner to Reference Example 8(a) but using 4-difluoromethoxy-3-(2-phenylethoxy)benzaldehyde [Reference Example 10(b)] there was prepared 4-difluoromethoxy-3-(2-phenylethoxy)benzoic acid as colourless crystals.

(b) By proceeding in a similar manner to Reference Example 8(a) but using 2-methoxy-5-methoxycarbonyl-benzaldehyde there was prepared 2-methoxy-5-methoxycarbonylbenzoic acid.

(i) By proceeding in a similar manner to Reference Example 8(a) but using 4-methoxy-3-[2-(pyridin-2-yl)ethynyl]benzaldehyde [Reference Example 23(a)] there was prepared 4-methoxy-3-[2-(pyridin-2-yl)ethynyl]benzoic acid which was recrystallised from methanol as a white crystalline solid, m.p. 228-229°C. [Elemental analysis:- C,71.06; H,4.40; N,5.51% Calculated for $C_{15}H_{11}NO_3$:- C,71.14; H,4.38; N,5.53%].

(j) By proceeding in a similar manner to Reference Example 8(a) but using 4-methoxy-3-(2-phenylethynyl)benzaldehyde [Reference Example 23(b)] there was prepared 4-methoxy-3-(2-phenylethynyl]benzoic acid which was recrystallised from acetonitrile as a white crystalline solid, m.p. 221-223°C. [Elemental analysis:- C,75.96; H,4.81% Calculated for $C_{16}H_{12}O_3$:- C,76.18; H,4.79%].

(k) By proceeding in a similar manner to Reference Example 8(a) but using 4-methoxy-3-[3-(2-thienyl)-1,2,4-oxadiazol-5-yl]methoxybenzaldehyde [Reference Example 9(g)] there was prepared 4-methoxy-3-[3-(2-thienyl)-1,2,4-oxadiazol-5-yl]methoxybenzoic acid as a white solid, m.p. 181-183°C.

(l) By proceeding in a similar manner to Reference Example 8(a) but using 4-methoxy-3-[2-(4-chlorophenyl)-1,3,4-oxadiazol-5-yl]methoxybenzaldehyde [Reference Example 9(h)] there was prepared 4-methoxy-3-[2-(4-chlorophenyl)-1,3,4-oxadiazol-5-yl]methoxybenzoic acid as a white solid, m.p. 251-253°C.

(m) By proceeding in a similar manner to Reference Example 8(a) but using 4-methoxy-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]methoxybenzaldehyde [Reference Example 9(i)] there was prepared 4-methoxy-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]methoxybenzoic acid as a white solid, m.p. 159-165°C.

REFERENCE EXAMPLE 9

(a) 3-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-ylmethoxy]-4-methoxybenzaldehyde

A stirred mixture of 3-hydroxy-4-methoxybenzaldehyde (0.69g), triphenylphosphine (1.79g) and 3-(4-chlorophenyl)-5-hydroxymethyl-1,2,4-oxadiazole [1.2g, Reference Example 4(a)] in dry tetrahydrofuran (30ml), under nitrogen, was treated dropwise with a solution of diisopropylazodicarboxylate (1.23ml) in dry tetrahydrofuran (30ml) over 1 hour. The reaction mixture was refluxed for 3 hours, then left standing at ambient temperature for 18 hours, then evaporated. The residue was recrystallised from methanol to give the title compound (1.45g) as colourless crystals, m.p. 125-129°C.

(b) By proceeding in a similar manner to Reference Example 9(a) but using 5-hydroxymethyl-3-(pyridin-2-yl)-1,2,4-oxadiazole [Reference Example 4(c)] there was prepared 4-methoxy-3-[3-(pyridin-2-yl)-1,2,4-oxadiazol-5-ylmethoxy]benzaldehyde as colourless crystals.

(c) By proceeding in a similar manner to Reference Example 9(a) but using 3-(2-hydroxyethyl)pyridine there was prepared 4-methoxy-3-[2-(pyridin-3-yl)ethoxy]-benzaldehyde as a yellow oil.

(d) By proceeding in a similar manner to Reference Example 9(a) but using 2-(2-hydroxyethyl)pyridine there was prepared

4-methoxy-3-[2-(pyridin-2-yl)ethoxyl-benzaldehyde as a pale yellow oil.

(e) By proceeding in a similar manner to Reference Example 9(a) but using 4-difluoromethoxy-3-hydroxybenzaldehyde and 2-(2-hydroxyethyl)-pyridine there was prepared 4-difluoromethoxy-3-[2-(pyridin-2-yl)ethoxylbenzaldehyde as a pale brown oil.

(g) By proceeding in a similar manner to Reference Example 9(a) but using 5-hydroxymethyl-3-(2-thienyl)-1,2,4-oxadiazole (Reference Example 4(d)) there was prepared 4-methoxy-3-[3-(2-thienyl)-1,2,4-oxadiazol-5-yl]methoxybenzaldehyde as a cream coloured solid, m.p. 93-97°C.

(h) By proceeding in a similar manner to Reference Example 9(a) but using 5-hydroxymethyl-2-(4-chlorophenyl)-1,3,4-oxadiazole (Reference Example 4(e)) there was prepared 4-methoxy-3-[2-(4-chlorophenyl)-1,3,4-oxadiazol-5-yl]methoxybenzaldehyde as a white solid, m.p. 155-157°C.

(i) By proceeding in a similar manner to Reference Example 9(a) but using 5-hydroxymethyl-3-(4-methoxyphenyl)-1,2,4-oxadiazole (Reference Example 4(f)) there was prepared 4-methoxy-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]methoxybenzaldehyde as a cream solid, m.p. 195-198°C.

REFERENCE EXAMPLE 10

(a) 4-Methoxy-3-(2-phenylethoxy)benzaldehyde

A mixture of 3-hydroxy-4-methoxybenzaldehyde (6g) and potassium carbonate (9.42g) in ethanol (40ml) was stirred at 60°C, for 0.5 hours, then it was treated dropwise with (2-bromoethyl)benzene (11.11g) during 40 minutes. The reaction mixture was stirred for 3.5 hours at 60°C, then it was heated at reflux overnight. The reaction mixture was cooled and then

evaporated, and the residue was partitioned between water (40ml) and dichloromethane (40ml). The organic phase was dried over magnesium sulphate and then concentrated. The resulting residue was dissolved in diethyl ether. The solution was washed with aqueous sodium hydroxide solution and then with water, then dried over magnesium sulphate and then evaporated to give the title compound (9.25g) as a yellow oil.

(b) By proceeding in a similar manner to reference Example 10(a) but using 4-difluoromethoxy-3-hydroxy-benzaldehyde there was prepared 4-difluoromethoxy-3-(2-phenylethoxy)benzaldehyde as colourless crystals.

REFERENCE EXAMPLE 11

(a) 4-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-ylmethoxy]-5-methoxypyridine-2-carboxylic acid

A mixture of methyl 4-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-ylmethoxy]-5-methoxypyridine-2-carboxylate [4.5g, Reference Example 13(a)] and aqueous potassium carbonate solution (1.82g in 50ml water) in methanol (200ml) was heated at reflux for 3.5 hours. The reaction mixture was partially evaporated to remove about 50ml of methanol then the thick suspension was treated with hydrochloric acid to adjust the pH of the mixture to between 1 and 2. The mixture was allowed to stand at ambient temperature for 18 hours, then cooled, then filtered. The solid was dried at 80°C under vacuum affording the title compound (2.19g) as colourless crystals.

(b) By proceeding in a similar manner to Reference Example 11(a) but using methyl 3-{2-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]ethyl}-4-methoxybenzoate [Reference Example 5(c)] there was prepared 3-{2-[3-(4-chlorophenyl-1,2,4-oxadiazol-5-yl]ethyl}-4-methoxybenzoic acid;

(c) By proceeding in a similar manner to Reference Example 11(a) but using methyl 5-methoxy-4-(2-[pyridin-3-yl]ethoxy)pyridine-2-carboxylate [7.54g, Reference Example 13(b)] there was prepared 5-methoxy-4-(2-[pyridin-3-yl]ethoxy)pyridine-2-carboxylic acid as a colourless solid.

(d) By proceeding in a similar manner to Reference Example 11(a) but using methyl 5-methoxy-4-(2-[pyridin-2-yl]ethoxy)pyridine-2-carboxylate [Reference Example 13(c)] there was prepared 5-methoxy-4-(2-[pyridin-2-yl]ethoxy)pyridine-2-carboxylic acid as a colourless solid.

(e) By proceeding in a similar manner to Reference Example 11(a) but using methyl 5-methoxy-4-(2-[4-methoxyphenyl]ethoxy)pyridine-2-carboxylate [8.66g, Reference Example 13(d)], there was prepared 5-methoxy-4-(2-[4-methoxyphenyl]ethoxy)pyridine-2-carboxylic acid as a colourless solid.

(f) By proceeding in a similar manner to Reference Example 11(a) but using methyl 4-methoxy-3-[3-(pyridin-4-yl)propyloxy]benzoate [Reference Example 21(a)] there was prepared 4-methoxy-3-[3-(pyridin-4-yl)propyloxy]benzoic acid which was recrystallised from methanol as colourless crystals, m.p. 166-167°C. [Elemental analysis:- C,66.61; H,5.97; N,4.75%. Calculated for $C_{16}H_{17}NO_4$:- C,66.88; H,5.97; N,4.87%].

(g) By proceeding in a similar manner to Reference Example 11(a) but using methyl 4-methoxy-3-[3-(pyridin-3-yl)propyloxy]benzoate [Reference Example 21(b)] there was prepared 4-methoxy-3-[3-(pyridin-3-yl)propyloxy]benzoic acid which was recrystallised from methanol as colourless crystals, m.p. 166-167°C. [Elemental analysis:- C,66.81; H,6.01; N,5.13%. Calculated for $C_{16}H_{17}NO_4$:- C,66.88; H,5.97; N,4.87%].

(h) By proceeding in a similar manner to Reference Example 11(a) but using methyl 4-methoxy-3-(phenoxymethyl)benzoate [Reference Example 21(c)] there was prepared 4-methoxy-3-(phenoxymethyl)benzoic acid as a yellow oil.

(i) By proceeding in a similar manner to Reference Example 11(a) but using methyl 4-methoxy-3-(benzyloxymethyl)benzoate [Reference Example 30] there was prepared 4-methoxy-3-(benzyloxymethyl)benzoic acid which was recrystallised from acetonitrile as colourless crystals.

(j) By proceeding in a similar manner to Reference Example 11(a) but using methyl 4-methoxy-3-(pyridin-2-yloxymethyl)benzoate [Reference Example 21(d)] there was prepared 4-methoxy-3-(pyridin-2-yloxymethyl)benzoic acid as a colourless solid.

(k) By proceeding in a similar manner to Reference Example 11(a) but using methyl 4-methoxy-3-(pyridin-2-ylmethoxy)benzoate [Reference Example 21(e)] there was prepared 4-methoxy-3-(pyridin-2-ylmethoxy)benzoic acid as a colourless solid, m.p. 215°C.

(l) By proceeding in a similar manner to Reference Example 11(a) but using methyl 4-methoxy-3-(pyridin-3-ylmethoxy)benzoate [Reference Example 21(f)] there was prepared 4-methoxy-3-(pyridin-3-ylmethoxy)benzoic acid as a colourless solid, m.p. 198°C.

(m) By proceeding in a similar manner to Reference Example 11(a) but using methyl 4-methoxy-3-(pyridin-4-ylmethoxy)benzoate [Reference Example 21(g)] there was prepared

4-methoxy-3-(pyridin-4-ylmethoxy)benzoic acid as a pale yellow solid, m.p. 201°C.

(n) By proceeding in a similar manner to Reference Example 11(a) but using methyl 4-methyl-3-(pyridin-2-ylethoxy)benzoate [Reference Example 21(h)] there was prepared 4-methyl-3-(pyridin-2-ylethoxy)benzoic acid as a pale yellow solid, m.p. 185°C.

REFERENCE EXAMPLE 12

(a) 3-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-4-methoxybenzoic acid

A solution of methyl 3-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]-4-methoxybenzoate [4.6g, Reference Example 5(d)] and potassium hydroxide (3.3g) in a mixture of methanol (200ml), water (100ml) and tetrahydrofuran (100ml) was refluxed for 7 hours then allowed to stand at ambient temperature for 3 days. The reaction mixture was evaporated. The residue was partitioned between water (300ml) and ethyl acetate (300ml). The aqueous phase was acidified by addition of 1N hydrochloric acid. The resulting solid was dried affording the title compound as a white solid.

(b) By proceeding in a similar manner to Reference Example 12(a) but using methyl 3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]-4-methoxybenzoate [Reference Example 5(e)] there was prepared 3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]-4-methoxybenzoic acid as a white solid m.p. 278-279°C. [Elemental analysis:- C,62.57; H,4.16; N,8.44%. Calculated:- C,62.58; H,4.32; N,8.58%];

(c) By proceeding in a similar manner to Reference Example 12(a) but using methyl 4-methoxy-3-(3-phenyl-1,2,4-oxadiazol-5-yl)-benzoate [Reference Example 5(f)] there was prepared

4-methoxy-3-(3-phenyl-1,2,4-oxadiazol-5-yl)-benzoic acid as a white solid m.p. 270-271°C. [Elemental analysis:- C,64.88; H,3.94; N,9.48%. Calculated:- C,64.87; H,4.08; N,9.45%];

(d) By proceeding in a similar manner to Reference Example 12(a) but using methyl 4-methoxy-3-(3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl)-benzoate [Reference Example 5(g)] there was prepared 4-methoxy-3-[3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl]-benzoic acid as a brown solid.

(e) By proceeding in a similar manner to Reference Example 12(a) but using methyl 4-methoxy-3-[2-(4-methoxyphenyl)ethenyl]benzoate [Reference Example 22] there was prepared 4-methoxy-3-[2-(4-methoxyphenyl)ethenyl]benzoic acid as a white solid.

(f) By proceeding in a similar manner to Reference Example 12(a) but using methyl 4-methoxy-3-benzylthiomethylbenzoate [Reference Example 26] there was prepared 4-methoxy-3-benzylthiomethylbenzoic acid as an off-white solid, m.p. 182-184°C.

REFERENCE EXAMPLE 13

(a) Methyl 4-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-ylmethoxyl-5-methoxypyridine-2-carboxylate

A stirred mixture of methyl 5-methoxy-4-pyridone-2-carboxylate (4.35g, prepared as described in WO 95/04045), triphenylphosphine (7.47g) and 3-(4-chlorophenyl)-5-hydroxymethyl-1,2,4-oxadiazole [5g, Reference Example 4(a)] in dry tetrahydrofuran (300ml), under nitrogen and at 60°C, was treated dropwise with a solution of diisopropylazodicarboxylate (5.14ml) in dry tetrahydrofuran (30ml) over 3.5 hours. The mixture was refluxed for 3 hours then left standing at ambient

temperature for 18 hours. The reaction mixture was evaporated. The residue was triturated with methanol to give the title compound (4.5g) as colourless crystals, m.p. 170-172°C.

(b) By proceeding in a similar manner to Reference Example 13(a) but using 3-(2-hydroxyethyl)pyridine there was prepared methyl 5-methoxy-4-(2-[pyridin-3-yl]ethoxy)pyridine-2-carboxylate as an oil, which was used without further purification.

(c) By proceeding in a similar manner to Reference Example 13(a) but using 2-(2-hydroxyethyl)pyridine there was prepared methyl 5-methoxy-4-(2-[pyridin-2-yl]ethoxy)pyridine-2-carboxylate as an orange oil, which was used without further purification.

(d) By proceeding in a similar manner to Reference Example 13(a) but using 4-methoxyphenethyl alcohol there was prepared methyl 5-methoxy-4-(2-[4-methoxyphenyl]ethoxy)-pyridine-2-carboxylate as a crude pale yellow solid, which was used without further purification.

REFERENCE EXAMPLE 14

N-(3,5-Dichloro-1-oxido-4-pyridinio)acetamide

A stirred mixture of peracetic acid (50ml) and hydrogen peroxide (5ml, 30% w/w solution in water), at 55-60°C, was treated portion-wise with N-(3,5-dichloropyridin-4-yl)acetamide (20.88g, Reference Example 15). The resulting solution was stirred at 55-60°C for a further 2 hours then allowed to cool to room temperature. The reaction mixture was added to ice (670g) and the mixture basified by treatment with a saturated aqueous solution of sodium bicarbonate. After standing at room temperature overnight the aqueous phase was separated from the insoluble material, and then continuously extracted with ethyl

acetate for 1 day. Evaporation of the extract gave the title compound (2.1g) as a white solid, m.p. 220-221°C. [Elemental analysis:- C,37.6;H,2.65;N, 12.5%. Calculated:- C,38.0;H,2.74; N,12.67%]. Further continuous extraction with ethyl acetate for 5 days gave a further quantity of the title compound (17.6g).

REFERENCE EXAMPLE 15

N-(3,5-Dichloropyridin-4-yl)acetamide.

A stirred solution of 4-amino-3,5-dichloropyridine (10.0g, prepared as described in the specification of International Patent Application Publication No. WO 92/12961), at 0°C, in dry tetrahydrofuran (75ml), under nitrogen, was treated with sodium hydride (5.5g, 60% dispersion in mineral oil, 138mmoles). After 15 minutes, the mixture was treated dropwise with a solution of freshly distilled acetyl chloride (5.35g) in dry tetrahydrofuran (10ml) and stirring was continued at 0°C for 1 hour. The mixture was allowed to warm to room temperature. After standing at room temperature overnight the mixture was treated with saturated aqueous ammonium chloride solution (100ml). The layers were separated, and the aqueous phase was extracted twice with dichloromethane (100ml). The combined organic phases were dried over sodium sulphate and then evaporated. The residue was triturated with t-butyl methyl ether and the insoluble material was recrystallised from ethyl acetate affording the title compound (7.75g) as an off-white solid, m.p. 172°C.

REFERENCE EXAMPLE 16

N-Acetyl-N-(3,5-dichloro-1-oxido-4-pyridinio)-4-difluoromethoxy-3-(2-phenylethoxy)benzamide

A stirred solution of N-(3,5-dichloro-1-oxido-4-pyridinio)acetamide (0.43g, Reference Example 14) in dry dimethylformamide (10ml) was treated with sodium hydride

(0.078g, 60% dispersion in mineral oil, 2mmoles), under nitrogen. After stirring at ambient temperature for 2.5 hours, the mixture was cooled to 10°C, then treated with a solution of 4-difluoromethoxy-3-(2-phenylethoxy)-benzoyl chloride [0.61g, Reference Example 7(g)] in dry dichloromethane (10ml). Stirring was continued at room temperature for 1.5 hours, then the reaction mixture was allowed to stand at room temperature for three days. The pH of the mixture was adjusted to 1 by treatment with concentrated hydrochloric acid. The mixture was then evaporated. The residue was dissolved in dichloromethane and this solution was washed with water and then evaporated. The residue was subjected to flash chromatography on silica gel, eluting with ethyl acetate, to give the title compound (0.2g) as colourless crystals.

REFERENCE EXAMPLE 17

Methyl 4-methoxy-3-[2-(pyridin-2-yl)ethoxy]benzoate

A suspension of 4-methoxy-3-[2-(pyridin-2-yl)ethoxy]benzoic acid [2.65g, Reference Example 8(d)] in anhydrous methanol (50ml), heated at reflux, was treated dropwise with concentrated sulphuric acid (5ml). After 5 hours the reaction mixture was cooled to room temperature, then treated with solid sodium bicarbonate until the solution was neutral, and then evaporated to a small volume. Saturated aqueous sodium bicarbonate solution (250ml), water (250ml) and dichloromethane (500ml) were added. The organic phase was separated and the aqueous phase was then extracted with dichloromethane (250ml). The combined organic phases were dried over sodium sulphate, and then evaporated. The residue was subjected to flash column chromatography on silica gel, eluting initially with mixtures of ethyl acetate and pentane (1:1 v/v then 7:3 v/v). The resulting light brown solid was recrystallised from t-butyl methyl ether, to give the title compound (0.57g) as a white crystalline solid, m.p. 86-88°C [Elemental analysis:- C,66.4; H,6.0; N,5.0%. Calculated:- C,66.9; H,6.0; N,4.9%].

REFERENCE EXAMPLE 18

2-(3,5-Dichloropyridin-4-yl)-1-[4-methoxy-3-[2-(pyridin-3-yl)ethoxy]phenyl]ethanol

A stirred solution of lithium diisopropylamide (10 mmoles) in dried tetrahydrofuran (25ml), under nitrogen, at -78°C, was treated with a solution of 3,5-dichloro-4-methylpyridine (1.47g) in dry tetrahydrofuran (25ml). After 2 hours the mixture was treated with a solution of 4-methoxy-3-[2-(pyridin-3-yl)ethoxy]benzaldehyde [2.33g, Reference Example 9(c)] in dry tetrahydrofuran (25ml). Stirring was continued for 2 hours, and then the reaction mixture was allowed to warm to room temperature. After standing at room temperature overnight, the reaction mixture was treated with saturated aqueous ammonium chloride solution and then extracted three times with dichloromethane (150ml). The combined extracts were dried over magnesium sulphate and then evaporated. The residual yellow oil was subjected to flash column chromatography on silica gel, eluting with ethyl acetate, affording the title compound as a thick yellow oil (1.74g).

REFERENCE EXAMPLE 19

(a) 3-(5-Methoxycarbonyl-2-methoxyphenyl)propionic acid

A mixture of 3-(5-methoxycarbonyl-2-methoxyphenyl)prop-2-enoic acid [4.72g, Reference Example 20] and 5% palladium on carbon (0.5g) was stirred under an atmosphere of hydrogen for one hour. The mixture was filtered through Hyflo supercel. The filtrate was evaporated affording the title compound (4.05g) as a colourless solid.

(b) By proceeding in a similar manner to Reference Example 19(a) but using 4-methoxy-3-[2-(pyridin-2-yl)ethynyl]benzoic acid [Reference Example 8(i)] there was prepared 4-methoxy-3-[2-(pyridin-2-yl)ethyl]benzoic acid, which was recrystallised from a mixture of acetonitrile and ethanol as a white

crystalline solid, m.p. 227-229°C. [Elemental analysis:- C,70.01; H,5.87; N,5.76%. Calculated for $C_{15}H_{15}NO_3$:- C,70.02; H,5.88; N,5.44%].

(c) By proceeding in a similar manner to Reference Example 19(a) but using 4-methoxy-3-(2-phenylethynyl)benzoic acid [Reference Example 8(j)] there was prepared 4-methoxy-3-(2-phenylethyl)benzoic acid as an off-white solid.

REFERENCE EXAMPLE 20

3-(5-Methoxycarbonyl-2-methoxyphenyl)prop-2-enoic acid

A mixture of 5-methoxycarbonyl-2-methoxybenzaldehyde (6.0g), malonic acid (3.81g) and piperidine (0.33ml) in ethanol (200ml) was heated at reflux for 2.5 hours, then allowed to stand at ambient temperature for 18 hours, and then refluxed for a further 2.5 hours. Further aliquots of malonic acid (3.81g) and piperidine (0.33ml) were added and then refluxing was continued for 30 hours. The reaction mixture was evaporated and the residue partitioned between ethyl acetate (100ml) and 1N sodium hydroxide (200ml). The aqueous phase was washed with ethyl acetate (100ml) then acidified to pH 1 by addition of hydrochloric acid. The resulting colourless solid was washed with water and dried to give the title compound (4.72g) as colourless crystals, m.p. 180-185°C.

REFERENCE EXAMPLE 21

(a) Methyl 4-methoxy-3-(3-pyridin-4-yl)propyloxybenzoate

A stirred mixture of methyl 3-hydroxy-4-methoxybenzoate (2g, prepared as described in WO 95/04045), triphenylphosphine (3.45g) and 4-pyridinepropanol (1.42ml) in dry tetrahydrofuran (120ml), under nitrogen, was treated dropwise with a solution of diisopropylazodicarboxylate (2.38ml) in dry tetrahydrofuran (60ml). The mixture was stirred at room temperature for 6 hours then left standing at ambient temperature for 18 hours.

The reaction mixture was evaporated to give the title compound as an orange solid which was used without further purification.

(b) By proceeding in a similar manner to Reference Example 21(a) but using 3-pyridinepropanol there was prepared methyl 4-methoxy-3-(3-pyridin-3-yl)propyloxybenzoate as an orange solid, which was used without further purification.

(c) By proceeding in a similar manner to Reference Example 21(a) but using phenol there was prepared methyl 4-methoxy-3-(phenoxymethyl)benzoate as a colourless oily solid, which was used without further purification.

(d) By proceeding in a similar manner to Reference Example 21(a) but using methyl 3-hydroxymethyl-4-methoxybenzoate and 2-hydroxypyridine there was prepared methyl 4-methoxy-3-(pyridin-2-yloxymethyl)benzoate as a yellow oil.

(e) By proceeding in a similar manner to Reference Example 21(a) but using 2-pyridylcarbinol there was prepared methyl 4-methoxy-3-(pyridin-2-ylmethoxy)benzoate as a white solid, m.p. 76°C.

(f) By proceeding in a similar manner to Reference Example 21(a) but using 3-pyridylcarbinol there was prepared methyl 4-methoxy-3-(pyridin-3-ylmethoxy)benzoate.

(g) By proceeding in a similar manner to Reference Example 21(a) but using 4-pyridylcarbinol there was prepared methyl 4-methoxy-3-(pyridin-4-ylmethoxy)benzoate as a brown oil.

(h) By proceeding in a similar manner to Reference Example 21(a) but using methyl 3-hydroxy-4-methylbenzoate (Reference Example 34) and 2-hydroxyethylpyridine there was prepared

methyl 4-methyl-3-(pyridin-2-ylethoxy)benzoate as a yellow oil, m.p. 113°C.

REFERENCE EXAMPLE 22

Methyl 4-methoxy-3-(2-(4-methoxyphenyl)ethenyl)benzoate

A stirred solution of 4-methoxybenzyl triphenylphosphonium chloride (3.56g) in dry methanol (350ml), under nitrogen, was treated with sodium hydride (0.44g, 50% dispersion in mineral oil) over 15 minutes. The mixture was then treated with methyl 3-formyl-4-methoxybenzoate (1.5g) and stirring was continued for 1 hour. The reaction mixture was stood at room temperature for 3 days then treated with sodium hydride (0.22g), then stirred for 8 hours, then treated with 4-methoxybenzyl triphenyl phosphonium chloride (0.65g) and then stirred for 18 hours. The mixture was evaporated and the residual brown oil was washed with diethyl ether to give the title compound as a rust coloured solid which was used without further purification.

REFERENCE EXAMPLE 23

(a) 4-Methoxy-3-[2-(pyridin-2-yl)ethynyl]benzaldehyde

A mixture of 4-methoxy-3-triflyloxybenzaldehyde (9.2g, Reference Example 24), 2-ethynylpyridine (5.1g) bis(triphenylphoshine)palladium(II) chloride (1.12g) and triethylamine (18ml) in dimethylformamide (90ml) was stirred at 85-90°C for 18 hours then cooled to room temperature and then treated with water (600ml). The pH of the mixture was adjusted to 6 by addition of concentrated hydrochloric acid then extracted twice with dichloromethane (150ml). The combined extracts were washed with brine then dried over magnesium sulphate and then evaporated. The residual black tar was washed twice with diethyl ether (250ml) and the combined washings were then evaporated. The residual brown solid was triturated with a mixture of ethyl acetate and pentane (1:1, v/v) to give the title compound as a brown solid.

(b) By proceeding in a similar manner to Reference Example 23(a) but using phenylacetylene there was prepared 4-methoxy-3-(2-phenylethynyl)benzaldehyde which was recrystallised from cyclohexane as yellow plates, m.p. 86-87°C.

REFERENCE EXAMPLE 24

4-Methoxy-3-triflyloxybenzaldehyde

A stirred solution of isovanillin (1.52g) in pyridine (15ml), under nitrogen, was cooled to -10°C then treated dropwise with triflic anhydride (1.68ml) over 85 minutes. The mixture was warmed to 0°C over 40 minutes then left at room temperature for 3 days. The reaction mixture was evaporated and the residue was triturated with ethyl acetate. The resulting white solid was washed with ethyl acetate and the washings were washed twice with brine (30ml) then dried over magnesium sulphate and then evaporated. The residual brown syrup was subjected to flash chromatography eluting with a mixture of ethyl acetate and pentane (1:1, v/v) to give the title compound as a straw coloured oil.

REFERENCE EXAMPLE 25

(a) 4-Methoxy-3-(2-naphthyl)benzoic acid

A stirred solution of 3-bromo-4-methoxybenzoic acid (1.9g) in dimethylformamide (40ml) was treated with tetrakistriphenylphosphine palladium(0) (0.3g). After stirring at room temperature for 15 minutes the mixture was treated with naphthalene-2-boronic acid (1.7g) and after stirring for a further 15 minutes the mixture was then treated with a solution of sodium carbonate (6g) in water (40ml). The mixture was then stirred for 1 hour at room temperature then heated at reflux for 22 hours. The reaction mixture was cooled then filtered and then diluted with water (50ml). The solution was washed twice with ethyl acetate (50ml), then the pH was adjusted to 4

by addition of dilute hydrochloric acid and then the solution was extracted four times with ethyl acetate (150ml). The combined extracts were evaporated to give the title compound as an off-white solid.

(b) By proceeding in a similar manner to Reference Example 25(a) but using benzofuran-2-boronic acid there was prepared 4-methoxy-3-(2-benzofuranyl)benzoic acid which was recrystallised from ethanol as grey coloured crystals, m.p. 267-268°C.

(c) By proceeding in a similar manner to Reference Example 25(a) but using naphthalene-1-boronic acid there was prepared 4-methoxy-3-(1-naphthyl)benzoic acid which was recrystallised from ethanol as a white solid.

(d) By proceeding in a similar manner to Reference Example 25(a) but using thiophene-3-boronic acid there was prepared 4-methoxy-3-(3-thienyl)benzoic acid which was recrystallised from ethanol as a silvery coloured solid.

(e) By proceeding in a similar manner to Reference Example 25(a) but using 4-methoxyphenylboronic acid there was prepared 4-methoxy-3-(4-methoxyphenyl)benzoic acid which was recrystallised from acetonitrile as white needles, m.p. 221-227°C.

REFERENCE EXAMPLE 26

Methyl 4-methoxy-3-(benzylthiomethyl)benzoate

A stirred solution of benzylmercaptan (0.75ml) in tetrahydrofuran (100ml), under nitrogen and at 0°C was treated with sodium hydride (0.45g). After stirring for 40 minutes the mixture was treated with methyl 3-bromomethyl-4-methoxybenzoate (1.5g, Reference Example 27) and this mixture allowed to warm

to room temperature then stirred for 8 hours and then stood for 24 hours. The reaction mixture was treated with further sodium hydride (0.2g) and benzyl mercaptan (0.5ml), stirred for 3 hours then poured into water (200ml). The mixture was extracted three times with ethyl acetate (50ml). The combined extracts were dried over magnesium sulphate then evaporated to give the title compound as a pale orange oil.

REFERENCE EXAMPLE 27

Methyl 3-bromomethyl-4-methoxybenzoate

A solution of methyl 4-methoxy-3-methylbenzoate (2.0g, Reference Example 28) and N-bromosuccinimide (2.2g) in chloroform (50ml) was treated with benzoyl peroxide (0.26g) and the mixture was heated at reflux for 5 hours then allowed to stand at room temperature for 18 hours. The reaction mixture was filtered and the filtrate was evaporated. The residual orange-red solid was dissolved in ethyl acetate and the solution was washed with water (50ml) then dried over magnesium sulphate and then evaporated. The residual light orange solid was recrystallised from methanol to give the title compound as a cream coloured solid, m.p. 122-125°C.

REFERENCE EXAMPLE 28

Methyl 4-methoxy-3-methylbenzoate

A stirred solution of 4-methoxy-3-methylbenzoic acid (7.5g, Reference Example 29) in methanol (200ml) was treated dropwise with acetyl chloride (2ml) and the mixture was heated at reflux. The reaction was followed by thin layer chromatography and when the reaction was complete the mixture was evaporated. The residue was dissolved in ethyl acetate (200ml) and the solution was washed with saturated sodium bicarbonate solution then dried over magnesium sulphate and then evaporated to give the title compound as a light brown solid, m.p. 66-68°C.

REFERENCE EXAMPLE 29

4-Methoxy-3-methylbenzoic acid

A solution of 3-methyl-4-methoxybenzaldehyde (10g) in acetone (470ml), at 40°C, was treated with a solution of potassium permanganate (18g) in water (40ml) over 45 minutes. The reaction mixture was cooled to room temperature then filtered. The filtrate was evaporated to remove the acetone and the remaining aqueous solution was acidified by addition of concentrated hydrochloric acid. The resulting solid was filtered and dried to give the title compound as an off-white solid, m.p. 193-198°C.

REFERENCE EXAMPLE 30

Methyl 4-methoxy-3-(benzyloxymethyl)benzoate

A stirred solution of methyl 3-hydroxymethyl-4-methoxybenzoate (3g) in dimethylformamide (100ml) was treated with sodium hydride (0.67g, 60% dispersion in mineral oil). After stirring at room temperature for 1 hour the mixture was treated dropwise with benzyl bromide (2ml), then stirred for 4 hours and then left standing at room temperature for 18 hours. The reaction mixture was evaporated. The residue was treated with water and the mixture extracted twice with dichloromethane (300ml). The combined extracts were evaporated and the residue was triturated with a mixture of tetrahydrofuran and diethyl ether then filtered. The filtrate was evaporate to give the title compound as a yellow oily solid.

REFERENCE EXAMPLE 31

Methyl 3-hydroxymethyl-4-methoxybenzoate

A suspension of methyl 3-formyl-4-methoxybenzoate (6g) in methanol (140ml) was treated portionwise with sodium borohydride (1.28g). The resulting solution was stirred at room temperature for 1.25 hours then treated with dilute hydrochloric acid (40ml, 1N). The mixture was evaporated to low volume then diluted with dichloromethane (250ml). The organic phase was separated, washed with water then dried over

magnesium sulphate and the evaporated to give the title compound as a colourless solid.

REFERENCE EXAMPLE 32

5-Acetoxymethyl-2-(4-chlorophenyl)-1,3,4-oxadiazole

A solution of N-(Acetoxyacetyl)-N'-(4-chlorobenzoyl)-hydrazine (5.8g, Reference Example 33) in toluene (200ml) was treated with 4-toluenesulphonic acid (0.4g) and the mixture was heated at reflux for 12 hours whilst removing water by means of a Dean and Stark condenser. After cooling the reaction mixture was washed twice with water (200ml) then diluted with diethyl ether (50ml) then dried over magnesium sulphate and then evaporated to give the title compound as a pale yellow solid. m.p. 46-48°C.

REFERENCE EXAMPLE 33

N-(Acetoxyacetyl)-N'-(4-chlorobenzoyl)hydrazine

A stirred solution of 4-chlorobenzoic hydrazide (6.76g) in a mixture of dichloromethane (125ml) and pyridine (25ml), under nitrogen, was treated with acetoxyacetyl chloride (4.5ml) over 10 minutes. After stirring for 1 hour at room temperature the reaction mixture was treated with dilute hydrochloric acid (300ml, 1N). The organic phase was separated then washed with dilute hydrochloric acid (300ml, 1N) then with saturated sodium bicarbonate solution (150ml) then twice with water (150ml and 200ml). The resulting suspension was filtered to give the title compound as white crystals, m.p. 174-176°C.

REFERENCE EXAMPLE 34

Methyl 3-hydroxy-4-methyl-benzoate

A stirred solution of 3-hydroxy-4-methylbenzoic acid (5g) in methanol (70ml) was treated dropwise with concentrated sulphuric acid (0.5ml) and the mixture was heated at reflux for 5 hours. The reaction mixture was treated with saturated sodium bicarbonate solution to give a solution of pH 7. The

mixture was evaporated. The residue was treated with water (100ml) then extracted twice with ethyl acetate (70ml). The combined extracts were washed with saturated sodium bicarbonate solution then dried over magnesium sulphate then treated with charcoal. The mixture was filtered. The filtrate was evaporated to give the title compound as a pale yellow solid, m.p. 113°C.

IN VITRO AND IN VIVO TEST PROCEDURES

1. Inhibitory effects of compounds on PDE IV activity

1.1 Preparation of PDE from guinea pig macrophages

The method is described in Turner et al. (Br. J. Pharmacol, 108 876-883, 1993). Briefly, cells were harvested from the peritoneal cavity of horse-serum treated (0.5ml i.p.) Dunkin Hartley guinea pigs (250-400g) and the macrophages purified by discontinuous (55%, 65%, 70% v/v) gradient (Percoll) centrifugation. Washed macrophages were plated out in cell culture flasks and allowed to adhere. The cells were washed with Hank's balanced salt solution, scraped from the flasks and centrifuged (1000 g). The supernatant was removed and the pellets stored at -80°C until use. The pellet was homogenised in 20mM tris(hydroxymethyl)aminomethane HCl, pH 7.5, 2mM magnesium chloride, 1mM dithiothreitol, 5mM ethylenediaminetetraacetic acid, 0.25mM sucrose, 20µM p-tosyl-1-lycine-chloromethyl-ketone, 10µg/ml leupeptin and 2000U/ml aprotinin.

1.2 Measurement of PDE activity

PDE activity was determined in macrophage homogenates by the two-step radioisotopic method of Thompson et. al., (Adv. Cyclic

Nucl. Res., 10, 69-92, 1979). The reaction mixture contained 20mM tris(hydroxymethyl)aminomethane HCl (pH 8.0), 10mM magnesium chloride, 4mM 2-mercaptoethanol, 0.2mM ethylenebis(oxyethylenenitrilo)tetraacetic acid and 0.05mg of bovine serum albumin/ml. The concentration of substrate was 1μM. The IC_{50} values (i.e. concentrations which produced 50% inhibition of substrate hydrolysis) for the compounds examined were determined from concentration-response curves in which concentrations ranged from 0.1nM to 40μM.

2. In vivo bronchodilator actions of compounds

2.1 Measurement of bronchodilatation

Bronchorelaxant activity are measured in in vivo tests in the anaesthetized guinea-pig or rat according to the method described in Underwood et al. (Pulm. Pharmacol. 5, 203-212, 1992) in which the effects on bronchospasm induced by histamine (or other spasmogens such as methacholine or leukotriene D_4) was determined. Compounds are administered orally 1 hour prior to administration of spasmogen.

3. Inhibitory effects of compounds against antigen-induced eosinophilia in the rat in vivo

3.1. Treatment of rats and measurement of eosinophil numbers

Male Brown Norway rats weighing 150-250g are sensitized on days 0, 12 and 21 with ovalbumin (100μg, i.p.). Rats are challenged on any one day between days 27-32.

24 hours and 1 hour before antigen challenge rats are dosed orally. Rats are challenged by exposure for 30 minutes to nebulized saline or ovalbumin (1 % in saline).

24 hours after challenge, rats are killed and the airways are lavaged with physiological salt solution. Total and differential cell counts are made.

4. In Vitro Inhibitory Effects on TNF-alpha Release by Human Monocytes

The effects of compounds on TNF-alpha production by human peripheral blood monocytes (PBMs) were examined as follows.

4.1. Preparation of blood mononuclear cells

Mononuclear cells (monocytes and lymphocytes) were obtained by centrifugation of heparinised whole blood on Histopaque-1077, and resuspending the mononuclear cell fraction in modified Hank's balanced salt solution. Mononuclear cells comprised 70-80% monocytes complemented by lymphocytes.

4.2. Measurement of TNF-alpha release

Purified mononuclear cells were spun down (200 g for 10 minutes at 20°C), resuspended at 10^6PBMs/ml of medium; RPMI 1640 containing 1%v/v FCS, 50U/ml penicillin and 50µg/ml streptomycin, and plated out in 96 well plates at 2 $x10^5$ cells/well. After incubating for 1.5 hours at 37°C in a 5% CO_2 incubator the medium (200µl) was changed to remove any non-adherent cells. One hour prior to challenge, the medium was changed to that containing compound for test or drug vehicle. Control treatments and compounds for test were assayed in quadruplicate wells. Compounds were tested within the concentration range of 3 x 10^{-10}M to 3 x 10^{-6}M. Medium (50µl) with or without 50ng/ml LPS (E. Coli, 055 B5 from Sigma, U.K.) was then added. The incubation was then

continued for a further 18 hours. Cell supernatants were removed for storage at -20°C.

TNF-alpha levels in cell supernatants were quantified using a standard sandwich ELISA technique. ELISA plates (Costar, U.K.) were coated overnight at 4°C with 3 mg/ml polyclonal goat anti-human TNF-alpha antibody (British Biotechnology, U.K.) in pH 9.9 bicarbonate buffer. Rabbit polyclonal anti-human TNF-alpha antiserum (Janssen Biochimicha, Belgium) at 1/500 dilution was used as the second antibody and polyclonal goat anti-rabbit IgG horseradish peroxidase (Calbiochem, U.S.A.) at 1/8000 dilution was used as the detection antibody. Color development was measured by absorbance at 450nm using a Titek plate reader.

TNF-alpha levels were calculated by interpolation from a standard curve using recombinant human TNF-alpha (British Biotechnology U.K.)(0.125-8ng/ml). Basal TNF-alpha levels were less than 100pg/ml whilst LPS stimulation of the PBMs increased TNF-alpha levels to 3-10ng/ml.

5. Inhibitory effects of compounds against antigen-induced bronchoconstriction in the anaesthetized rat in vivo

5.1. Treatment of rats and measurement of antigen-induced bronchoconstriction

Male Brown Norway rats weighing 150-250g are sensitized on days 0, 12 and 21 with ovalbumin (100µg, i.p.). Rats are challenged on any one day between days 27-32.

24 hours and 1 hour before antigen challenge rats are dosed orally. Rats are anaesthetized to allow recording of lung function (airway resistance and lung compliance) using respiratory mechanics software. Rats are challenged with

ovalbumin i.v. and the peak changes in airway resistance and lung compliance are determined.

6. Inhibitory effects of compounds on serum TNF-alpha levels in LPS-challenged mice

6.1. Treatment of animals and measurement of murine TNF-alpha

Female Balb/c mice (age 6-8 weeks, weight 20-22g from Charles River, U.K.) in groups of five or more animals were dosed p.o. with compounds suspended in 1% (w/v) carboxymethyl cellulose : 0.2% Tween 80 in PBS then challenged after a minimum period of 30 min with 30µg of LPS i.p. After 90 minutes the animals were killed by carbon dioxide asphyxiation and bled by cardiac puncture. Blood was allowed to clot at 4°C, centrifuged (12,000 g for 5 minutes) and serum taken for TNF-alpha analysis. TNF-alpha levels were measured using a commercially available murine TNF-alpha ELISA kit, purchased from Genzyme (Cat.no.1509.00), as recommended by the manufacturer. Values for TNF-alpha were calculated from a recombinant murine TNF-alpha standard curve.

7. Streptococcal Cell Wall-Induced Arthritis in Rats

7.1 Preparation of S. pyogenes purified cell wall

Purified S. pyogenes cell wall is prepared from the cell pellet of a log-phase culture of S. pyogenes, group A, strain D-58. The whole bacteria are homogenized by grinding with glass beads and the crude cell wall collected by centrifugation and subsequently washed with 2% SDS in PBS followed by PBS to remove contaminating proteins and nucleic acids. The cell wall is further purified by sonication and differential centrifugation to obtain a purified preparation which pelleted at 100,000 x g. This material is suspended in sterile PBS and

the quantity of cell wall determined by measuring the rhamnose content of the preparation (purified cell wall contains 28% rhamnose by weight). The material is filtered through a 0.22 µm filter and stored at 4°C until used for arthritis induction

7.2 Arthritis Induction and measurement of joint diameters

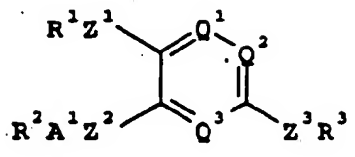
Female Lewis rats weighing 140-160 g are injected intra-articularly into the left or right tibio-tarsal joint on day 0 with purified S. pyogenes cell wall (10µg in 10µl sterile saline). On day 20, rats receive an intravenous injection of purified cell wall (100µg in 100 µl sterile saline) via the lateral vein of the tail. Joint diameters are measured with calipers across the lateral and medial malleoli of the previously intra-articularly injected joint immediately prior to the i.v. injection and then daily through day 24. The net joint diameter is determined by subtracting the value for the contralateral joint. Body weights are also measured daily. Compounds or vehicle are administered by oral gavage on days 20-23. Typically, 8-10 animals are used per group. For each dose, the total daily dose is divided into two equal aliquots which are given at approximately 9 a.m. and 3 p.m.

The value of the compounds of the invention is enhanced by their very low mammalian toxicity levels.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof.

CLAIMS

1. A compound of formula (I)



(I)

wherein

R^1 represents a straight- or branched-chain alkyl group of 1 to about 6 carbon atoms, optionally substituted by one or more halogen atoms, or when Z^1 is a direct bond R^1 may also represent a hydrogen atom;

R^2 represents an optionally substituted aryl, partially saturated bicycloaryl, heteroaryl or R^aR^bN- group;

R^3 represents an optionally substituted aryl or heteroaryl group;

A^1 represents a direct bond, a straight- or branched-chain alkylene linkage containing from 1 to about 6 carbon atoms optionally substituted by halogen, hydroxyl, alkoxy or oxo, or A^1 represents a straight- or branched-carbon chain comprising from 2 to about 6 carbon atoms and contains a double or triple carbon-carbon bond, or is interrupted by an oxygen or sulphur atom, a phenylene, imino (-NH-) or alkylimino linkage, or a sulphinyl or sulphonyl group;

Z^1 represents an oxygen or sulphur atom or a direct bond;

Z^2 represents an oxygen or sulphur atom or a direct bond;

Z^3 represents a -C≡C-, $-CH_2-CZ-$, $-CZ-CH_2-$, -CZ-CZ-, $-CH_2-NH-$, $-CH_2-O-$, $-CH_2-S-$, $-CH_2-SO-$, $-CH_2-SO_2-$, $-CF_2-O-$, -CZ-NH-, $-NH-CH_2-$, $-O-CH_2-$, $-S-CH_2-$, $-SO-CH_2-$, $-SO_2-CH_2-$, $-O-CF_2-$, -O-CZ-, -NH-CZ-, -N=N-, $-NH-SO_2-$, $-SO_2-NH-$,

-CZ-CZ-NH-, -NH-CO-O-, -O-CO-NH-, -C(=NOR^c)CH$_2$-, -C(F)=N-, -CH(F)-CH$_2$- or -NH-CO-NH- linkage;

Z represents an oxygen or sulphur atom;

R^a and R^b each independently represents an alkyl or arylalkyl group, or NR^{a}R^b forms a 4-6 membered cyclic amine which optionally contains an additional heteroatom selected from O, S, NH or NR^c, or is substituted with an oxo group;

R^c represents an alkyl or arylalkyl group;

Q^1, Q^2 and Q^3, which may be the same or different, each represents a CH or CX^1 linkage or a nitrogen atom; and

X^1 represents a halogen atom;

and N-oxides thereof, and their prodrugs, pharmaceutically acceptable salts, and solvates (e.g. hydrates), thereof;

but excluding compounds of formula (I) where R^1 represents a straight- or branched-chain alkyl group of 1 to about 4 carbon atoms substituted by one or more fluorine atoms, R^2 represents a phenyl group, R^3 represents an optionally substituted phenyl or pyridyl group, A^1 represents methylene group, Q^1, Q^2 and Q^3 each represent a CH linkage, Z^1 and Z^2 each represent an oxygen atom, and Z^3 represents a -CO-NH- linkage, and compounds of formula (I) where R^1 represents methyl, ethyl, difluoromethyl or trifluoromethyl, R^2 represents a phenyl group optionally substituted with C$_{1-4}$alkyl, C$_{1-4}$alkoxy or halogen, R^3 represents an optionally substituted aryl or heteroaryl group, A^1 represents a C$_{1-6}$alkylene (optionally substituted by halogen, hydroxy or alkoxy), a -OC$_{2-6}$alkylene, or a -NHC$_{2-6}$alkylene linkage, Q^1, Q^2 and Q^3 each represent a CH linkage, Z^1 and Z^2 each represent an oxygen atom, and Z^3 represents a -CH$_2$-O-, -CH$_2$-NH-, -CH$_2$-S-, -O-CH$_2$-,

-S-CH_2-, -NH-CH_2-, -CH_2-CO-, -CO-CH_2-, -CO-NH-, -O-CO- or -NH-CO- linkage.

2. A compound according to claim 1 in which Z^1 represents an oxygen atom and R^1 represents a straight- or branched-chain alkyl group of 1 to about 6 carbon atoms, optionally substituted by one or more halogen atoms.

3. A compound according to claim 1 or claim 2 in which Q^1 and Q^3 are CH and Q^2 is CH, CF, N or N(O).

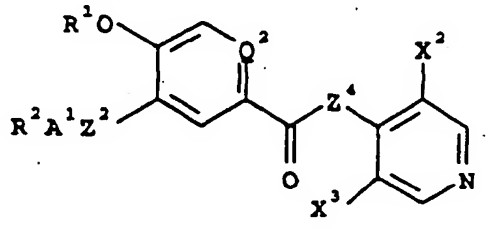
4. A compound according to any previous claim in which Z^3 represents -CO-NH-, -CO-CH_2-, -C(F)=N- or -CH(F)-CH_2-.

5. A compound according to any previous claim in which R^3 represents an optionally substituted azaheteroaryl group, or an N-oxide thereof.

6. A compound according to claim 5 in which R^3 represents pyridyl substituted by one or more halogen atoms, or an N-oxide thereof.

7. A compound according to claim 6 in which R^3 represents 3,5-dichloropyrid-4-yl, or an N-oxide thereof.

8. A compound of formula (Ia)



(Ia)

wherein

R^1 represents a straight- or branched-chain alkyl group of 1 to about 6 carbon atoms, optionally substituted by one or more halogen atoms;

R^2 represents an optionally substituted aryl, a partially saturated bicycloaryl, an optionally substituted heteroaryl group, or a substituted oxadiazole ring, or a R^aR^bN- group (wherein R^a and R^b are as defined in Claim 1);

A^1 represents a direct bond, a straight- or branched-chain alkylene linkage containing from 1 to about 6 carbon atoms optionally substituted by halogen, hydroxyl, alkoxy or oxo, or A^1 represents a straight- or branched-carbon chain comprising from 2 to about 6 carbon atoms and contains a double or triple carbon-carbon bond, or is interrupted by an oxygen or sulphur atom, a phenylene, imino (-NH-) or alkylimino linkage, or a sulphinyl or sulphonyl group;

Z^2 represents an oxygen or sulphur atom or a direct bond;

Z^4 represents NH or CH_2;

Q^2 represents a CH or CX^1 linkage or a nitrogen atom; and

X^1, X^2 and X^3 each represent a halogen atom;

and N-oxides thereof, and their prodrugs, pharmaceutically acceptable salts, and solvates (e.g. hydrates), thereof;

but excluding compounds of formula (Ia) where R^1 represents a straight- or branched-chain alkyl group of 1 to about 4 carbon atoms substituted by one or more fluorine atoms, R^2 represents a phenyl group, A^1 represents methylene group, Q^2 represents a CH linkage, Z^2 represents an oxygen atom, and Z^4 represents NH, and compounds of formula (Ia) where R^1 represents methyl, ethyl, difluoromethyl or trifluoromethyl, R^2 represents a phenyl group optionally substituted with C_{1-4}alkyl, C_{1-4}alkoxy or halogen, A^1 represents a C_{1-6}alkylene (optionally substituted by halogen, hydroxy or alkoxy), a

-OC_{2-6}alkylene, or a -NHC_{2-6}alkylene linkage, Q^2 represents a CH linkage, Z^2 represents an oxygen atom, and Z^4 represents NH or CH_2.

9. A compound according to any previous claim in which R^1 represents a C_{1-4}alkyl group optionally substituted by one or more halogen atoms.

10. A compound according to any previous claim in which R^2 represents an optionally substituted heteroaryl group.

11. A compound according to claim 10 in which R^2 represents an optionally substituted thienyl, thiazolyl or pyridyl group or a substituted 1,2,4-oxadiazole or a substituted 1,3,4-oxadiazole group.

12. A compound according to claim 11 in which R^2 represents 1,2,4-oxadiazol-5-yl or 1,3,4-oxadiazol-5-yl each substituted in the 3- or 2-position respectively by an optionally substituted phenyl group or a heteroaryl group.

13. A compound according to claim 12 in which R^2 represents 3-heteroaryl-1,2,4-oxadiazol-5-yl group.

14. A compound according to claim 13 in which R^2 represents 3-(2-pyridyl)-1,2,4-oxadiazol-5-yl group.

15. A compound according to any of the claims 1-9 in which R^2 represents an optionally substituted aryl group.

16. A compound according to claim 15 in which R^2 represents phenyl or 4-methoxyphenyl.

17. A compound according to any of the claims 1-9 in which R^2 represents a 2-indanyl group.

18. A compound according to any previous claim in which R^3 represents 3,5-dichloropyrid-4-yl or 3,5-dichloro-1-oxido-4-pyridinio.

19. A compound according to any previous claim in which A^1 represents a straight chain C_{1-4}alkylene linkage or a straight chain C_{3-4}alkylene linkage interrupted by an oxygen atom.

20. A compound according to any previous claim in which Z^2 is an oxygen atom or a direct bond.

21. A compound according to any previous claim in which Q^1 and Q^3 are CH and Q^2 is CH, N or N(O).

22. A compound according to claim 8 in which R^1 is methyl or difluoromethyl, R^2 is a 3-(2-pyridyl)-1,2,4-oxadiazol-5-yl group, X^2 and X^3 each represent a chlorine atom and A^1, Q^2, Z^2 and Z^4 are as defined in any previous claim.

23. N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(4-phenylbutoxy)benzamide;
N-(3,5-dichloropyridin-4-yl)- 4-methoxy-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-ylmethoxy)benzamide;
3-(benzylthiomethyl)-N-(3,5-dichloropyridin-4-yl)-4-methoxybenzamide;
N-(3,5-dichloropyridin-4-yl)-3-[3-(pyridin-2-yl)-1,2,4-oxadiazol-5-ylmethoxy]-4-methoxybenzamide;
4-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-ylmethoxy]-N-(3,5-dichloropyridin-4-yl)-5-methoxypyridine-2-carboxamide;

N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(pyridin-2-yloxymethyl)benzamide;
3-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-ylmethoxy]-N-(3,5-dichloro-pyridin-4-yl)-4-methoxybenzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(3-methyl-1,2,4-oxadiazol-5-ylmethoxy)benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[2-(pyridin-4-yl)ethoxy]benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-(4-methylthiazol-5-yl)ethoxy)benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-thien-2-ylethoxy)benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-benzyloxybenzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(4-phenylbutoxy)benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[2-(pyridin-3-yl)propyloxy]benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-benzyloxyethoxy)benzamide;
3-(2-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]ethyl)-N-(3,5-dichloropyridin-4-yl)-4-methoxybenzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(2-phenylethoxy)benzamide;
N-(3,5-dichloropyridin-4-yl)-4-difluoromethoxy-3-(2-phenylethoxy)benzamide;
N-(3,5-dichloropyridin-4-yl)-5-methoxy-4-[2-(4-methoxyphenyl)ethoxy]pyridine-2-carboxamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[2-(pyridin-2-yl)ethoxy]benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[2-(pyridin-3-yl)ethoxy]benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-phenylethyl)benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-phenylethynyl)benzamide;

N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(phenoxymethyl)benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(benzyloxymethyl)benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(4-methoxyphenyl)benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[3-(2-thienyl)-1,2,4-oxadiazol-5-yl]methoxybenzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[2-(4-chlorophenyl)-1,3,4-oxadiazol-5-yl]methoxybenzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]methoxybenzamide;
3-[3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-N-(3,5-dichloropyridin-4-yl)-4-methoxybenzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(3-phenyl-1,2,4-oxadiazol-5-yl)benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[3-(pyridin-2-yl)-1,2,4-oxadiazol-5-yl]benzamide;
N-(3,5-dichloropyridin-4-yl)-5-methoxy-4-(2-[pyridin-3-yl]ethoxy)pyridine-2-carboxamide;
N-(3,5-dichloropyridin-4-yl)-5-methoxy-4-(2-[pyridin-2-yl]ethoxy)pyridine-2-carboxamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-[3-(pyridin-4-yl)propyloxy]benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-[3-(pyridin-3-yl)propyloxy]benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-[2-(4-methoxyphenyl)ethenyl]benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-[2-(pyridin-2-yl)ethynyl]benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-[2-(pyridin-2-yl)ethyl]benzamide;

N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(2-naphthyl)benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(2-benzofuranyl)benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(1-naphthyl)benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(3-thienyl)benzamide;
2-(3,5-dichloropyridin-4-yl)-1-{4-methoxy-3-[2-(pyridin-2-yl)ethoxy]phenyl}ethanone;
2-(3,5-dichloropyridin-4-yl)-1-{4-methoxy-3-[2-(pyridin-3-yl)ethoxy]phenyl}ethanone;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(4-methoxybenzyl)benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(3-(4-methoxyphenyl)propyl)benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(4-methoxyphenylthiomethyl)benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(pyridin-2-ylmethoxy)benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(pyridin-3-ylmethoxy)benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-(pyridin-4-ylmethoxy)benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methyl-3-(pyridin-2-ylethoxy)benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-{2-(1-piperidinyl)ethoxy}benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-{2-(2-oxo-pyrrolidin-1-yl)ethoxy}benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-phenoxyethoxy)benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-{2-(3-methylpyridin-2-yl)ethoxy}benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-furyl)benzamide;

N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-indanyloxy)benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-[2-(2-furyl)ethoxy]benzamide;
N-(3,5-dichloropyridin-4-yl)-3-[2-(pyridin-2-yl)ethyl]benzamide;
(3,5-dichloropyridin-4-yl)-N-[fluoro(3-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-ylmethoxy]-4-methoxyphenyl)methylene]amine;
(3,5-dichloropyridin-4-yl)-N-[fluoro(4-methoxy-3-(3-methyl-1,2,4-oxadiazol-5-ylmethoxy)phenyl)methylene]amine;
(3,5-dichloropyridin-4-yl)-N-[fluoro-(4-methoxy-3-[2-pyridin-4-ylethoxy]phenyl)-methylene]amine;
(3,5-dichloropyridin-4-yl)-N-[fluoro(4-methoxy-3-[2-(4-methylthiazol-5-yl)ethoxy]phenyl)methylene]amine;
(3,5-dichloropyridin-4-yl)-N-[fluoro-(4-methoxy-3-[2-thien-2-ylethoxy]phenyl)-methylene]amine;
(3,5-dichloropyridin-4-yl)-N-[fluoro-(4-methoxy-3-[benzyloxy]phenyl)-methylene]amine;
(3,5-dichloropyridin-4-yl)-N-[fluoro-(4-methoxy-3-[4-phenylbutoxy]phenyl)-methylene]amine;
(3,5-dichloropyridin-4-yl)-N-[fluoro-(4-methoxy-3-[(3-pyridin-3-yl)propyloxy]phenyl)-methylene]amine;
(3,5-dichloropyridin-4-yl)-N-[fluoro-(4-methoxy-3-[2-benzyloxyethoxy]phenyl)-methylene]amine;
(3,5-dichloropyridin-4-yl)-N-[fluoro-(4-methoxy-3-[2-piperidinylethoxy]phenyl)-methylene]amine;
2-(3,5-dichloro-pyridin-4-yl)-1-(3-(pyridin-2-ylethoxy)-4-methoxyphenyl)-1-fluoroethane;
and N-oxides, and pharmaceutically acceptable salts and solvates (e.g. hydrates) thereof.

24. N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-phenylethoxy)benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(4-phenylbutoxy)benzamide;

N-(3,5-dichloropyridin-4-yl)-4-difluoromethoxy-3-[2-phenylethoxy]benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-benzyloxyethoxy)benzamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-phenoxyethoxy)benzamide;
N-(3,5-dichloropyridin-4-yl)-5-methoxy-4-[2-(4-methoxyphenyl)ethoxy]pyridine-2-carboxamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-indanyloxy)benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-[2-(pyridin-2-yl)ethoxy]benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-[3-(pyridin-4-yl)propyloxy]benzamide;
N-(3,5-dichloro-pyridin-4-yl)-4-methoxy-3-[3-(pyridin-3-yl)propyloxy]benzamide;
N-(3,5-dichloropyridin-4-yl)-5-methoxy-4-[2-(pyridin-2-yl)ethoxy]pyridine-2-carboxamide;
N-(3,5-dichloropyridin-4-yl)-4-methoxy-3-(2-thien-2-ylethoxy)benzamide;
3-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-ylmethoxy]-N-(3,5-dichloropyridin-4-yl)-4-methoxybenzamide;
3-[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-ylmethoxy]-N-(3,5-dichloropyridin-4-yl)-4-methoxybenzamide;
N-(3,5-dichloro-pyridin-4-yl)-3-[3-(pyridin-2-yl)-1,2,4-oxadiazol-5-ylmethoxy]-4-methoxybenzamide;
3-[2-(4-chlorophenyl)-1,3,4-oxadiazol-5-ylmethoxy]-N-(3,5-dichloropyridin-4-yl)-4-methoxybenzamide;
and N-oxides, and pharmaceutically acceptable salts and solvates (e.g. hydrates) thereof.

25. A pharmaceutical composition comprising a compound as claimed in claim 1 in association with a pharmaceutically acceptable carrier or excipient.

26. A compound of formula (I) as claimed in any preceding claim for use in therapy.

27. A compound of formula (I) as claimed in any preceding claim for use in the treatment of a patient suffering from, or subject to, a condition which can be ameliorated by the administration of an inhibitor of TNF.

28. A compound of formula (I) as claimed in any preceding claim for use in the treatment of a patient suffering from, or subject to, a condition which can be ameliorated by the administration of an inhibitor of type IV cyclic AMP phosphodiesterase.

29. A composition as claimed in Claim 25 for use in the treatment of a patient suffering from, or subject to, a condition which can be ameliorated by the administration of an inhibitor of TNF.

30. A composition as claimed in Claim 25 for use in the treatment of a patient suffering from, or subject to, a condition which can be ameliorated by the administration of an inhibitor of type IV cyclic AMP phosphodiesterase.

31. Use of a compound of formula (I) as claimed in any preceding claim in the manufacture of a medicament for the treatment of a patient suffering from, or subject to, a condition which can be ameliorated by the administration of an inhibitor of TNF.

32. Use of a compound of formula (I) as claimed in any preceding claim in the manufacture of a medicament for the treatment of a patient suffering from, or subject to, a condition which can be ameliorated by the administration of an inhibitor of type IV cyclic AMP phosphodiesterase.

33. A method for the treatment of a human or animal patient suffering from, or subject to, a condition which can be ameliorated by the administration of an inhibitor of TNF or of type IV cyclic AMP phosphodiesterase comprising administering to said patient an effective amount of a compound of formula (I) as claimed in any preceding claim.

34. A compound substantially as hereinbefore described with reference to the Examples.

INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/GB 96/01746

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D213/81 C07D213/75 C07D213/89 C07D213/61 C07D401/12
C07D405/12 C07D409/12 C07D413/12 C07D413/14 C07D417/12
A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	EP,A,0 706 795 (PFIZER) 17 April 1996 see the whole document ---	1-34
X,P	WO,A,95 20578 (RHONE POULENC RORER LTD ;FENTON GARRY (GB); PALFREYMAN MALCOLM NOR) 3 August 1995 see page 165, line 32 - line 33 see page 168, line 15 - line 16; claims ---	1-34
X	WO,A,94 12461 (PFIZER ;DUPLANTIER ALLEN J (US); EGGLER JAMES F (US); MARFAT ANTHO) 9 June 1994 cited in the application see claims; examples 177,178 --- -/--	1-34

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 October 1996	23.10.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Bosma, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter · nal Application No
PCT/GB 96/01746

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,95 01338 (BYK GULDEN LOMBERG CHEM FAB ;AMSCHLER HERMANN (DE)) 12 January 1995 cited in the application see page 19; claims; example 14	1-34
X	WO,A,94 02465 (RHONE POULENC RORER LTD) 3 February 1994 see Reference examples 11, 71 see page 149, line 32 - line 33	1-34
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, no. 11, 1994, WASHINGTON US, pages 1696-1703, XP002015726 M.J. ASHTON ET AL.: "Inhibitors as antiasthmatic agents. The syntheses and biological activities of 3-(cyclopentyloxy)-4-methoxybenzamides and analogs." see compound 10c	1-34
A	WO,A,92 12961 (RHONE POULENC RORER LTD) 6 August 1992 cited in the application see claims; examples	1-34
X	BIOORGANIC & MEDICAL CHEMISTRY LETTERS, vol. 5, no. 17, 1995, OXFORD, pages 1969-1972, XP000605692 J.B. CHENG ET AL.: "Synthesis and in vitro profile of a novel series of catechol benzimidazoles. The discovery of potent, selective phosphodiesterase type IV inhibitors with greatly attenuated affinity for the (3H)rolipram binding site." see Scheme I, compounds 6	1-34
X	ARZNEIMITTEL FORSCHUNG DRUG RESEARCH., vol. 37, no. 7, 1987, AULENDORF DE, pages 854-859, XP002015994 S. GOENECHEA ET AL.: "Isolation and identification of chlorphenoxamine metabolites in human urine." see page 857, column 1, line 21 - line 22	1,2
X	BULLETIN DE LA SOCIETE CHIMIQUE DE FRANCE 2 PARTIE - CHIMIE ORGANIQUE, BIOCHIMIE., vol. 9-10, 1977, PARIS FR, pages 901-905, XP002016007 R. MARTIN: "Studies on the Fries reaction. XIV. Mechanisms developed in acid-catalyzed reactions. IV. Preparation of 5-acylguaiacols." see CAS RN 66475-99-8	1,2

-/--

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB 96/01746

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 112, no. 5, 29 January 1990 Columbus, Ohio, US; abstract no. 36227z, M.D. ROZWADOWSKA: "Synthesis of secoisoquinoline alkaloids." page 618; XP002016008 see CAS RN 124465-50-5 see abstract & POLISH JOURNAL OF CHEMISTRY, vol. 62, no. 7-12, 1988, WARSAW, pages 793-798, ---	1,2
X	TETRAHEDRON LETTERS, vol. 36, no. 16, 17 April 1995, OXFORD GB, pages 2713-2716, XP002016011 T.A. ENGLER ET AL.: "Cycloaddition reactions of 1,4-benzoquinone mono- and bisimides with styrenyl systems:" see ref. 9. compound v see page 2716 -----	1,2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB96/01746

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 33 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The subject matter of the present application is so broad that a complete search is not possible on economic grounds. Therefore the search has been based on the examples and the claims as indicated
Claims searched incompletely: 1,3-7,10-21,25-33

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ..onal Application No
PCT/GB 96/01746

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0706795	17-04-96	US-A-	5563143	08-10-96
		AU-A-	3177295	04-04-96
		CA-A-	2158632	22-03-96
		JP-A-	8134073	28-05-96
WO-A-9520578	03-08-95	AU-A-	1463195	15-08-95
WO-A-9412461	09-06-94	AU-A-	5539694	22-06-94
		CA-A-	2150812	09-06-94
		CN-A-	1094028	26-10-94
		CZ-A-	9501417	15-11-95
		EP-A-	0672031	20-09-95
		FI-A-	935379	03-06-94
		HU-A-	65928	28-07-94
		JP-T-	8501318	13-02-96
		NO-A-	952178	01-08-95
		NZ-A-	257955	28-05-96
		PL-A-	309257	02-10-95
		ZA-A-	9308978	01-06-95
WO-A-9501338	12-01-95	AU-A-	7490794	24-01-95
		CA-A-	2165192	12-01-95
		EP-A-	0706513	17-04-96
		FI-A-	956333	29-12-95
		HU-A-	73232	29-07-96
		NO-A-	955211	21-12-95
		PL-A-	311820	18-03-96
WO-A-9402465	03-02-94	AU-A-	4717693	14-02-94
		CA-A-	2140441	03-02-94
		EP-A-	0652868	17-05-95
		FI-A-	950375	27-01-95
		HU-A-	72656	28-05-96
		JP-T-	8503925	30-04-96
		NO-A-	950319	27-03-95
		NZ-A-	254881	25-09-96
		PL-A-	307265	15-05-95
		ZA-A-	9305448	19-05-94
WO-A-9212961	06-08-92	AT-T-	132134	15-01-96

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/GB 96/01746

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9212961		AU-B-	664694	30-11-95
		AU-A-	1188192	27-08-92
		AU-A-	4565196	02-05-96
		CA-A-	2101423	29-07-92
		CZ-A-	9301528	13-04-94
		DE-D-	69207017	08-02-96
		DE-T-	69207017	05-09-96
		EP-A-	0497564	05-08-92
		EP-A-	0569414	18-11-93
		EP-A-	0669311	30-08-95
		ES-T-	2081563	01-03-96
		HU-A-	64942	28-03-94
		JP-T-	6504782	02-06-94
		NZ-A-	241427	26-08-94
		PL-B-	169994	30-09-96
		SK-A-	80993	08-12-93
		ZA-A-	9200547	03-05-93

Form PCT/ISA/210 (patent family annex) (July 1992)